Nanoscience and Nanotechnology Research at the NIH

U.S. Department of
Health & Human Services

Jeffery A. Schloss, Ph.D.
Program Director,
Technology Development Coordination
National Human Genome Research Institute, NIH

NIBIB-DOE Workshop
Biomedical Applications of Nanotechnology
Bethesda, March 17, 2005

NHGRI

Mission: To uncover new knowledge...
...that will lead to better health for everyone;
...to help prevent, detect, diagnose, and treat
disease and disability.

Nanoscience and nanotechnology refer to
research and development
at the atomic, molecular, or macromolecular levels,
at a scale of about 1 – 100 nm,
providing a fundamental understanding of
phenomena and materials at this scale and
creating and using structures, devices and systems
that have novel properties and functions
because of their small size.

Unique opportunities

1. Nanotechnology operates at the same scale as biological processes, offering an entirely unique vantage point from which to view and interact with the fundamental biology of life.

- Most other technologies require the study of large numbers of molecules purified away from the cells and tissues in which they actually function; nanotechnology will offer ways to study, quantitatively, how individual molecules and assemblies of molecules work inside of cells.
- Those studies at the nanoscale will enable understanding of the *design* of biological systems and processes.
- That knowledge of component and system design is needed for, and will emerge from, quantitative modeling of biology.
- The design information will change the way we think about biology and medicine. Moreover, it will have implications for materials and systems design that have nothing to do with biology ("biomimetics").

Unique opportunities - 2

2. Materials, devices and tools currently emerging from other disciplines provide opportunities to approach the study of biology and disease mechanisms, and the diagnosis and treatment of disease, in powerful new ways:

- miniaturization (but that's only the beginning…)
- sensitivity
- selectivity
- new concepts

Outline

- Administrative
  - BECON
  - Funding
- Examples of NIH-supported nanosci/tech
- What biology brings to nanotech
- NIH Roadmap
- Conclusion

NANOTECHNOLOGY RESEARCH AT NIH

Nanotechnology Research at the NIH

is coordinated through the

NIH Bioengineering Consortium

BECON

NIH BIOENGINEERING CONSORTIUM (BECON)

BECON MEMBERS

NIH-OER	NCRR	NIAMS	NIEHS
NIH-CSR	NEI	NIBIB	NIGMS
NIH-OIR	NHGRI	NICHD	NIMH
NIH-CC	NHLBI	NIDA	NINDS
NIH-ORS	NIA	NIDCD	NINR
NIH-CIT	NIAAA	NIDCR	NLM
NCI	NIAID	NIDDK	*DOE NSF NIST*

Biomedical Engineering At The NIH - Netscape

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National Institutes of Health
Bioengineering Consortium

NIBIB Home

BECON Home

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NIH Bioengineering Consortium (BECON)

Bioengineering Consortium

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Symposia
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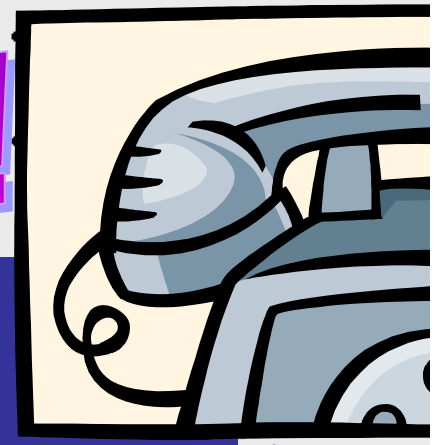
Contact Program Directors in the Institutes!



Your portal to bioengineering

grants & programs at NIH

http://www.becon.nih.gov

What's New?

BECON - The Bioengineering Consortium (BECON) is the focus of bioengineering activities at the NIH. The Consortium coordinates representatives from all the NIH Institutes and Centers and develops policy for the Institute of

and
Solicitation

This Web Site - This Web site contains information about the structure and

Applet QLTMenu running

NIH NANOSCIENCE/NANOTECHNOLOGY NANOMEDICINE NCI ALLIANCE CONTACTS

National Cancer Institute	Dan Gallahan, Ed Monachino
NCI Alliance for Nanotechnology	Greg Downing, Travis Earles
National Eye Institute	Richard Fisher, Paul Sieving
National Heart, Lung, and Blood Institute	Denis Buxton
National Human Genome Research Institute	Jeff Schloss, Allison Peck
National Institute on Aging	Winifred K. Rossi
National Inst of Alcohol Abuse and Alcoholism	Karen Peterson
National Inst of Allergy and Infectious Diseases	Maria Giovanni
Nat'l Inst of Arthritis & Musculosk & Skin Diseases	Jim Panagis, Kuan Wang
National Institute for Biomedical Imaging and Bioengineering	Bill Heetderks, Peter Moy
National Inst of Child Health and Human Development	Louis Quatrano
National Inst on Deafness and Other Communication Disorders	Roger Miller
National Inst of Dental and Craniofacial Research	Eleni Kousvelari
National Inst of Diabetes and Digestive and Kidney Disorders	Maren Laughlin
National Institute on Drug Abuse	Tom Aigner
National Institute of Environmental Health Sciences	David Balshaw, Sally Tinkle
National Toxicology Program	John Bucher, Nigel Walker
National Institute of General Medical Sciences	Cathy Lewis
National Institute of Mental Health	Mike Huerta
Nat'l Inst of Neurological Disorders and Stroke	Joe Pancrazio
Center for Scientific Review	John Bowers
Clinical Center	King Li

NIH BIOENGINEERING CONSORTIUM (BECON)

http://
www.becon.nih.gov/
becon_symposia.htm

Nanoscience and Nanotechnology:

Shaping Biomedical Research

June 2000

Symposium Report

National Institutes of Health
Bioengineering Consortium


Catalyzing
Team Science
June 23-24, 2003
Natcher Conference Center
National Institutes of Health
Bethesda, Maryland
http://www.becon.nih.gov/symposium2003.htm
Bioengineering Consortium National Institutes of Health Department of Health and Human Services

NANOTECHNOLOGY RESEARCH SUPPORT AT NIH

NIH supports nanoscience and nanotechnology research in the context of many programs.

While in some of those programs/projects, the focus may be on the nano-research *per se*, in other cases the nano-research may be a component of a larger project with broader goals.

Several examples are provided here, to demonstrate support for the breadth of potential applications of nanotechnology for understanding, diagnosing and treating disease.

NANOTECHNOLOGY RESEARCH SUPPORT AT NIH

Program announcements issued through BECON:

- Nanoscience and Nanotechnology in Biology and Medicine
- Bioengineering Nanotechnology Initiative (SBIR)
- Exploratory/Developmental Bioengineering Research Grants
- Bioengineering Research Grants
- Bioengineering Research Partnerships
- Mentored Quantitative Research Career Development (K25)
- ***Awards under these programs are listed on the BECON web site.***

NANOTECHNOLOGY RESEARCH SUPPORT AT NIH

BECON

Nanoscience and Nanotechnology in Biology and Medicine

- i) create & use structures, devices & systems that have novel properties and functions because of their small size, to achieve a fundamental understanding of biological processes or for disease detection, therapy, or prevention; ii) conceive, fabricate and test devices to detect and analyze nanoscale entities of relevance to biomedicine; iii) study biological systems at the nanoscale to develop nanotechnologies and nanostructured materials for use in biomedicine.
- Encourages team approach to nanotechnology research
- R01 (research project) & R21 (exploratory/developmental) if little preliminary data and potential for groundbreaking impact. R21s are for up to 3 years, up to $125,000 per year direct cost
- Review panel dedicated to this program announcement
- Application Receipt: February 18 and August 18, through 2006
- http://grants.nih.gov/grants/guide/pa-files/PAR-03-045

NANOTECHNOLOGY RESEARCH SUPPORT AT NIH

BECON

Bioengineering Nanotechnology Initiative (SBIR)

- Nanotechnology is emerging as a field critical for enabling essential breakthroughs that may have tremendous potential for affecting biomedicine.
- Encourages team approach to nanotechnology research
- Phase I may request up to two years, $200,000 per year
- Phase II may request up to three years, $400,000 per year
- Applications Receipt per SBIR:
  April 1, August 1 and December 1
- Competes with other SBIR applications
- http://grants.nih.gov/grants/guide/pa-files/PA-02-125

BIOENGINEERING RESEARCH SUPPORT AT NIH

BECON

Bioengineering Research Partnerships

- For basic and applied research by a multi-disciplinary team applying an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior.
- Partnership must include bioengineering expertise and basic biology and/or clinical expertise.
- Identify lead investigators in Abstract
- Maximum request = $2M per year for five years
- Need approval >6 wks before submission if request >$500,000 direct cost
- Research Project (R01) mechanism
- Application receipt: January 21, August 20 (2004 through 2006)
- http://grants.nih.gov/grants/guide/pa-files/PAR-04-023.html

Reviewed in Special Emphasis Panels

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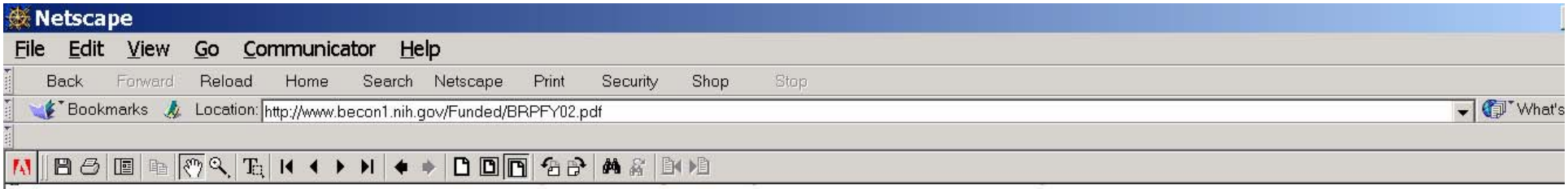
BIOENGINEERING RESEARCH SUPPORT AT NIH

BECON

Bioengineering Research Partnerships



31. **Principal Investigator:** Mcknight, Timothy **Affiliation:** UT-BATTELLE, LLC-OAK RIDGE NATIONAL LAB
Project Title: Nano Arrays for Real-Time Probing Within Living Cells
Grant Number: 1-R01-EB-433-1-A1 **Funding Organization:** NIBIB
Abstract:

This project will exploit the recent development of rigid, vertically aligned, carbon nanofiber arrays to provide nanoscale probes for mapping intra and extracellular molecular events in and around living cells in real time with extremely high spatial resolution (< 50 nm probing areas). Devices will be fabricated and characterized to determine the performance of nanoscale arrays as independently addressable electrochemical molecular probes. Characterizations will be performed using a set of standard analytes that have been routinely used for characterization of carbon-based electrode systems (year 1). Probe response to hydrogen peroxide and superoxide anion will then be characterized (year 1 into year 2). Strategies and methods will then be develop for coupling nanofiber arrays around individual and groups of living cells (year 2). Electrochemical analysis techniques will be applied at individual elements of carbon nanofiber arrays to spatially and temporally map the activity of peroxide around and ultimately within individual cell locales (year 3). This research will be structured around development of these methodologies using microfluidic-based cell and analyte handling strategies, thereby promoting future high-throughput screening applications, such as clinical diagnostics of cell and tissue specimens and pharmaceutical exploration and discovery. This effort will be conducted by various organizational groups within the Oak Ridge National Laboratory. The Interdisciplinary team involved with this effort features mechanical and electrical engineers with experience in microfluide systems/semiconductor/and nanoscale fabrication, a biochemist and biologist with expertise in cell culture and single cell monitoring, analytical chemists, and a biophysicist, with expertise in cell signaling and environmental response. This effort will directly address BRP thrust areas including nanotechnology and microtechnology, functional genomics/microarray technology/gene expression analysis, cell and molecular imaging, and complex biological systems.

BIOENGINEERING RESEARCH SUPPORT AT NIH

BECON

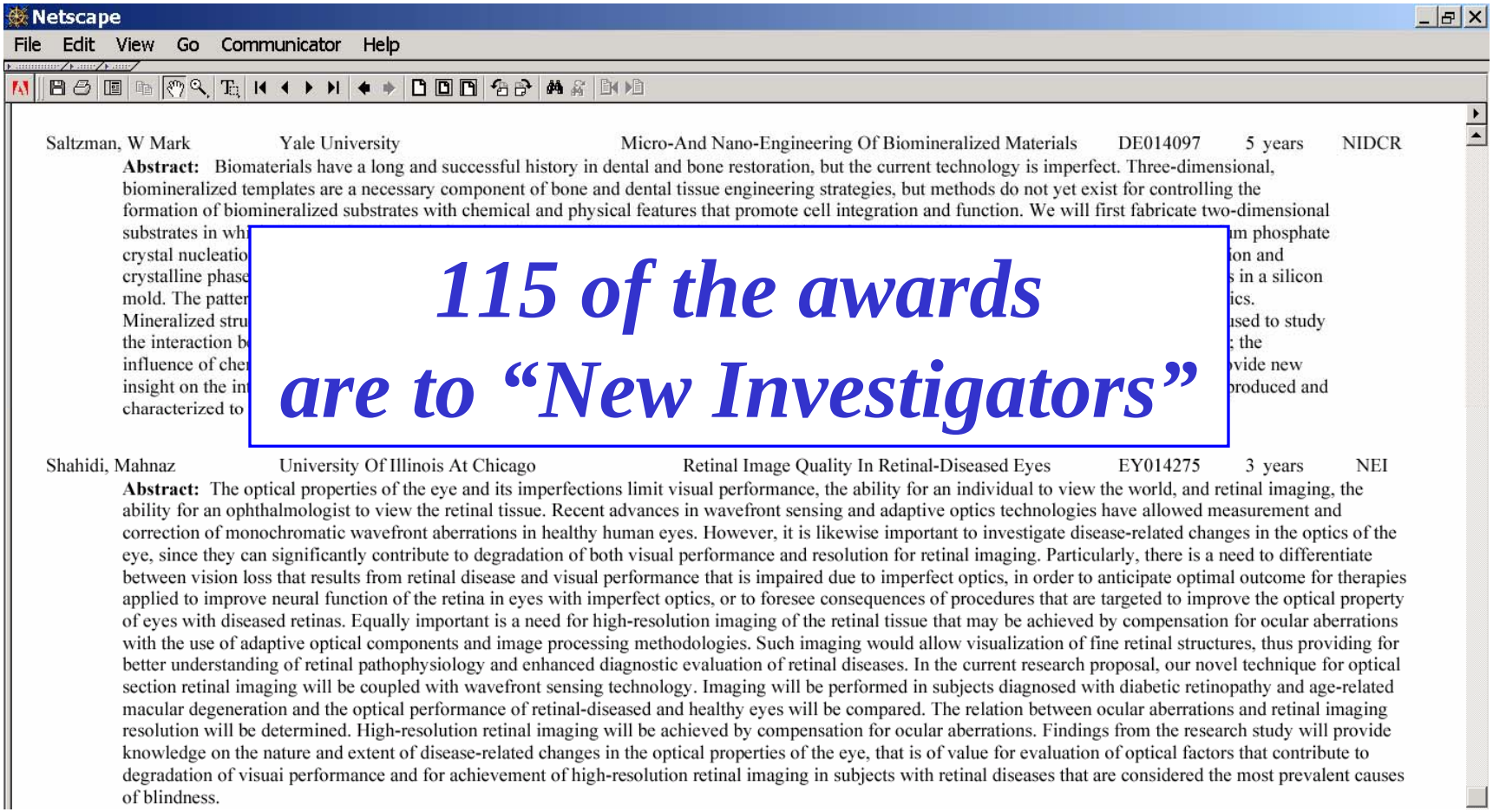
Bioengineering Research Grants

- For basic and applied multi-disciplinary research that addresses important biological or medical research problems.
- Hypothesis-driven, discovery-driven, developmental, or design-directed research.
- Multi-disciplinary research performed in a single laboratory or by a small number of investigators that applies an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior.
- Research Project (R01) mechanism
- Applications Receipt: February 1, June 1, and October 1
- http://grants.nih.gov/grants/guide/pa-files/PA-02-011.html
  (will be re-issued)

BIOENGINEERING RESEARCH SUPPORT AT NIH

BECON

Bioengineering Research Grants
275 funded since FY 99 (through FY2004)
http://www.becon.nih.gov/Funded/BRG_200X.pdf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Saltzman, W Mark Yale University Micro-And Nano-Engineering Of Biomineralized Materials DE014097 5 years NIDCR

Abstract: Biomaterials have a long and successful history in dental and bone restoration, but the current technology is imperfect. Three-dimensional, biomineralized templates are a necessary component of bone and dental tissue engineering strategies, but methods do not yet exist for controlling the formation of biomineralized substrates with chemical and physical features that promote cell integration and function. We will first fabricate two-dimensional substrates in wh… …m phosphate crystal nucleatio… …ion and crystalline phase… …s in a silicon mold. The patter… …ics. Mineralized stru… …sed to study the interaction b… …; the influence of che… …vide new insight on the in… …roduced and characterized to …

115 of the awards are to "New Investigators"

Shahidi, Mahnaz University Of Illinois At Chicago Retinal Image Quality In Retinal-Diseased Eyes EY014275 3 years NEI

Abstract: The optical properties of the eye and its imperfections limit visual performance, the ability for an individual to view the world, and retinal imaging, the ability for an ophthalmologist to view the retinal tissue. Recent advances in wavefront sensing and adaptive optics technologies have allowed measurement and correction of monochromatic wavefront aberrations in healthy human eyes. However, it is likewise important to investigate disease-related changes in the optics of the eye, since they can significantly contribute to degradation of both visual performance and resolution for retinal imaging. Particularly, there is a need to differentiate between vision loss that results from retinal disease and visual performance that is impaired due to imperfect optics, in order to anticipate optimal outcome for therapies applied to improve neural function of the retina in eyes with imperfect optics, or to foresee consequences of procedures that are targeted to improve the optical property of eyes with diseased retinas. Equally important is a need for high-resolution imaging of the retinal tissue that may be achieved by compensation for ocular aberrations with the use of adaptive optical components and image processing methodologies. Such imaging would allow visualization of fine retinal structures, thus providing for better understanding of retinal pathophysiology and enhanced diagnostic evaluation of retinal diseases. In the current research proposal, our novel technique for optical section retinal imaging will be coupled with wavefront sensing technology. Imaging will be performed in subjects diagnosed with diabetic retinopathy and age-related macular degeneration and the optical performance of retinal-diseased and healthy eyes will be compared. The relation between ocular aberrations and retinal imaging resolution will be determined. High-resolution retinal imaging will be achieved by compensation for ocular aberrations. Findings from the research study will provide knowledge on the nature and extent of disease-related changes in the optical properties of the eye, that is of value for evaluation of optical factors that contribute to degradation of visuai performance and for achievement of high-resolution retinal imaging in subjects with retinal diseases that are considered the most prevalent causes of blindness.

NANOTECHNOLOGY RESEARCH SUPPORT AT NIH

Tissue Engineering

Functional Tissue Engineering of Musculoskeletal Tissues

- To stimulate innovative research that will enhance our understanding of functional tissue engineering of musculoskeletal tissues (articular cartilage, ligaments, tendons, bone, meniscus, intervertebral disc and skeletal muscle).
- NIAMS, NICHD, NIDCR
- http://grants.nih.gov/grants/guide/pa-files/PA-02-014.html

Novel Approaches to Corneal Tissue Engineering

- To explore new approaches that could lead to enhanced engineering of corneal tissues, includes studies of early developmental processes to delineate the interactions between individual corneal tissue layers, the biomechanical properties of the stroma, cellular control of matrix deposition, control of corneal growth and maturation, and studies of synthetic replacement materials.
- NEI
- http://grants.nih.gov/grants/guide/pa-files/PA-02-053.html

NANOTECHNOLOGY RESEARCH SUPPORT AT NIH

Diagnostics & Therapeutics

Novel Technologies for *in vivo* Imaging (R21)

- For the development and delivery of novel image acquisition or enhancement technologies and methods for biomedical imaging and image-guided interventions and therapy, and which may incorporate limited pilot or clinical feasibility evaluations using either pre-clinical models or clinical studies. This initiative will facilitate the proof-of-feasibility, development, and delivery of novel imaging technologies and limited evaluation studies to show proof-of-concept and functionality.
- NCI
- http://grants.nih.gov/grants/guide/pa-files/PA-04-095.html

Speech Processor Optimization for Cochlear Implants (R21 and R01)

- To advance the design of speech processors for cochlear implants. The goal of this RFA is to support the development of innovation and enhancements for cochlear implants that will increase the level of patient performance. The research may involve conceptualization, design, fabrication, and/or testing of algorithms for evoking neural activity with cochlear implants.
- NIDCD
- http://grants.nih.gov/grants/guide/rfa-files/RFA-DC-04-001.html

NANOTECHNOLOGY RESEARCH SUPPORT AT NIH

NHLBI Programs of Excellence in Nanotechnology

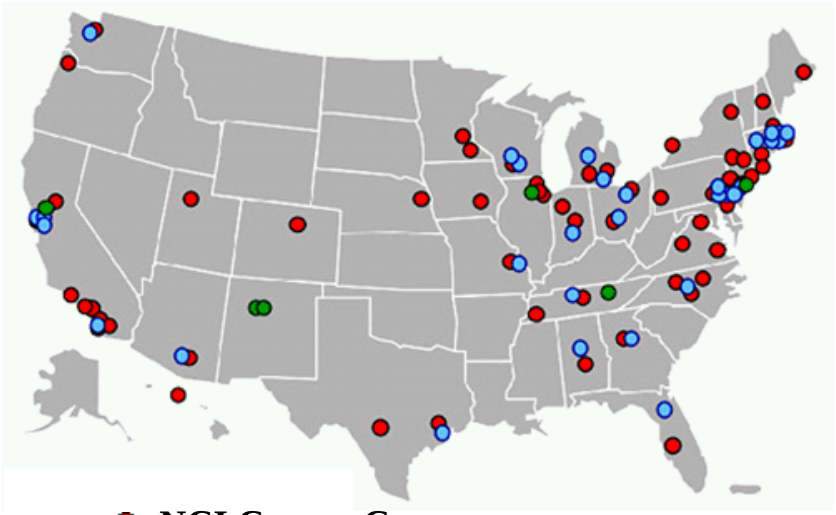
- multidisciplinary teams capable of developing and applying nanotechnology and nanoscience solutions to the diagnosis and treatment of cardiovascular, pulmonary, hematopoietic and sleep disorders.
- foster partnerships between the nanotechnology and the heart, lung, blood, and sleep disorder (HLBS) research communities.
- partial list of potential applications: tissue repair and cellular replacement; targeted probes to detect vulnerable atherosclerotic plaque and target delivery of therapy; inhaled biosensors for early diagnosis of pro-inflammatory signals in the lung; in vivo sensors of O_2 blood concentrations and heart functions to detect problems during sleep, detection and inactivation of blood pathogens…
- U01 network, 3 - 4 awards, 5 yrs, program investment $6 M FY05, $12 M FY06→
- LOI Receipt: June 23, 2004 Application Receipt: July 21, 2004
- http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-020.html

NANOTECHNOLOGY RESEARCH SUPPORT AT NIH

NCI Alliance for Nanotechnology in Cancer

Key Opportunities – Platforms

- Molecular Imaging and Early Detection
- *In Vivo* Imaging
- Reporters of Efficacy
- Multifunctional Therapeutics
- Prevention and Control
- Research Enablers



- **NCI Cancer Centers**
- **NCI-Funded Nanotech Projects**
- **DOE Nanoscale Science Research Centers**

Cancer Nanotechnology Strategies

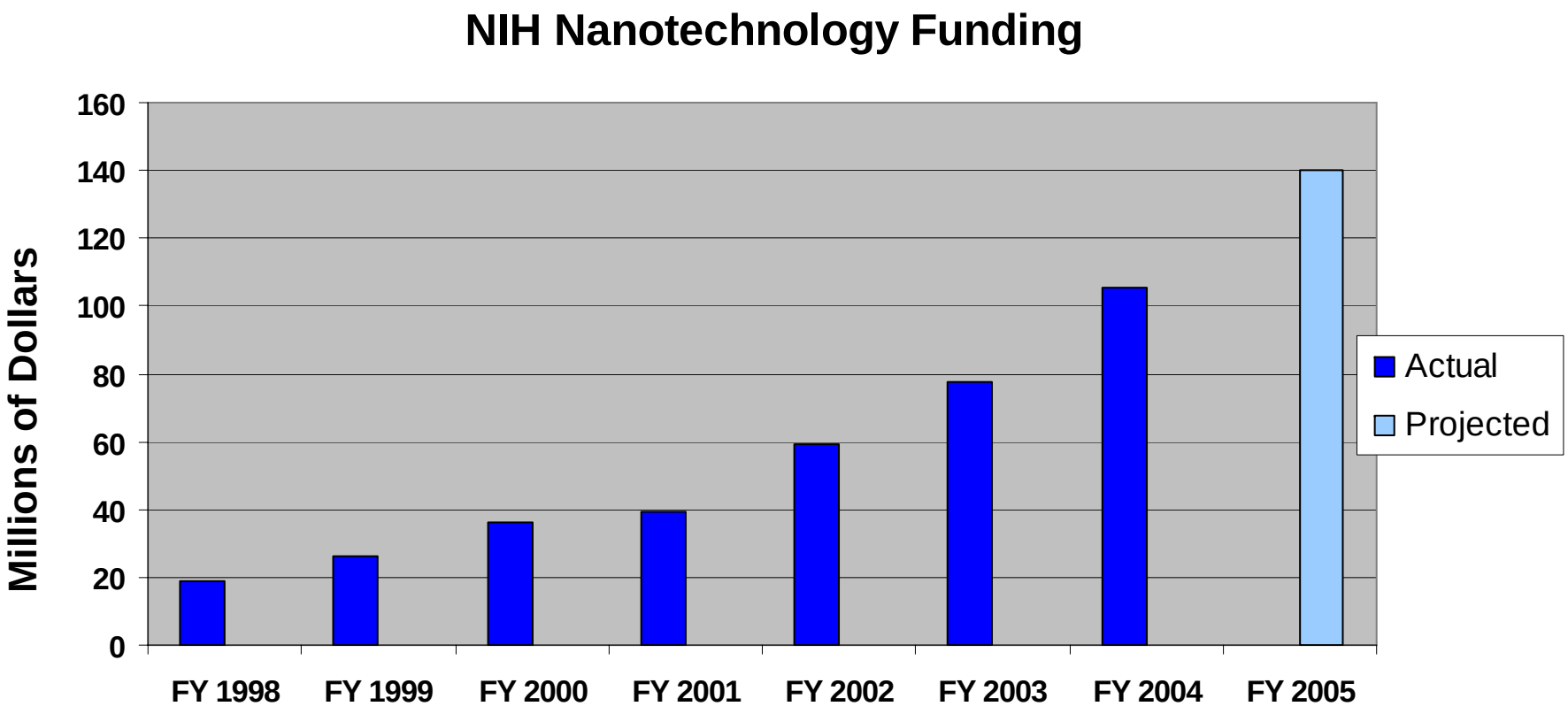
- Centers of Cancer Nanotechnology Excellence
- Nanotechnology Characterization Laboratory
- Building Research Teams (training and research)
- Creating Platforms – Directed Programs
- Basic and Applied Research Initiatives

http://nano.cancer.gov/

NANOTECHNOLOGY RESEARCH SUPPORT AT NIH

Emerging Programs – National Toxicology Program

- RFP Announcement: Studies to evaluate the toxic and carcinogenic potential of test agents in laboratory animals via inhalation exposure for the National Toxicology Program, RFP NIH-ES-04-07
- Release date: February 27, 2004.
- "The contract is designed to study diverse agents that may include: abrasive blasting agents, quantum dots, carbon nanotubes, metal working fluids, or other agents."
- Expected release date of the RFP is approximately March 8, 2004 with proposals due May 7, 2004.
- http://grants.nih.gov/grants/guide/notice-files/NOT-ES-04-006.html

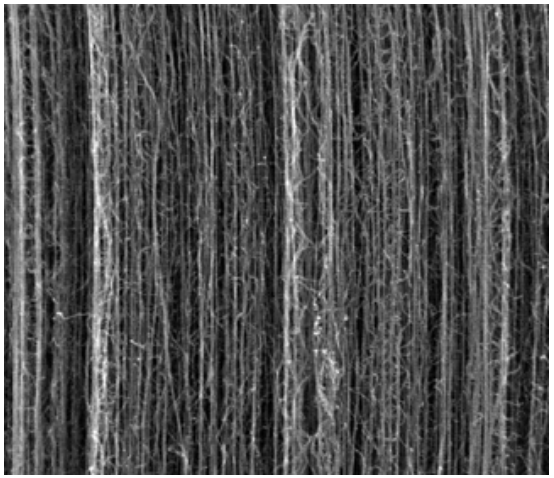

NIH Nanotechnology Funding
Millions of Dollars
160
140
120
100
80
60
40
20
0
FY 1998
FY 1999
FY 2000
FY 2001
FY 2002
FY 2003
FY 2004
FY 2005
Actual
Projected

National Nanotechnology Initiative (NNI) Grand Challenge for Healthcare

BECON

- Detecting Disease *Before* Health Has Deteriorated
  - Imaging
  - Sensors
- Implants to Replace Worn or Damaged Body Parts
  - Controlling interactions of synthetic and inorganic materials with the body, for effective integration
- Delivery Of Therapeutics
  - Particle Size
  - Targeting
- Research Tool correlates of the above

Sensors

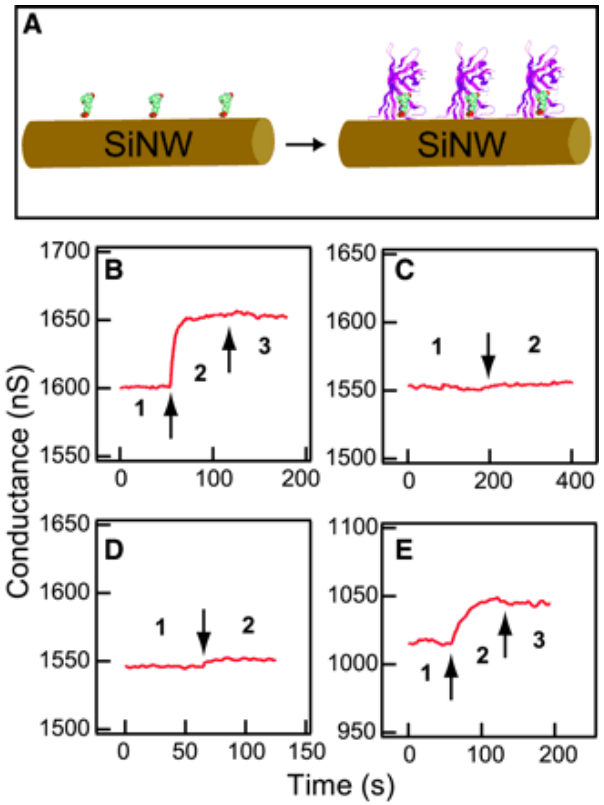


NASA AMES RESEARCH CENTER

Meyya Meyyappan, Ph.D.

NASA Ames Research Center

Carbon nanotubes (CNT) exhibit unique electronic and extraordinary mechanical properties. Ames has grown CNT, only 1 nm in diameter in the form of films and aligned bundles, and is currently making an effort to grow vertical tubes of controlled length for sensor development. The tip of the nanotubes will be functionalized with appropriate probe molecules for diagnostics. A prototype catheter will be developed which would permit detection of specific oligonucleotide sequences that serve as molecular signatures of cancer cells.



Real-time detection of protein binding: biotin-modified SiNW and subsequent binding of streptavidin (drawn approximately to scale). (B) region 2 corresponds to the addition of 250 nM streptavidin, (E) 25 pM streptavidin.

Y. Cui, Q. Wei, H. Park & C.M. Lieber, Science, 2001, *293*:1289-1292.

NANOSYS, INC.

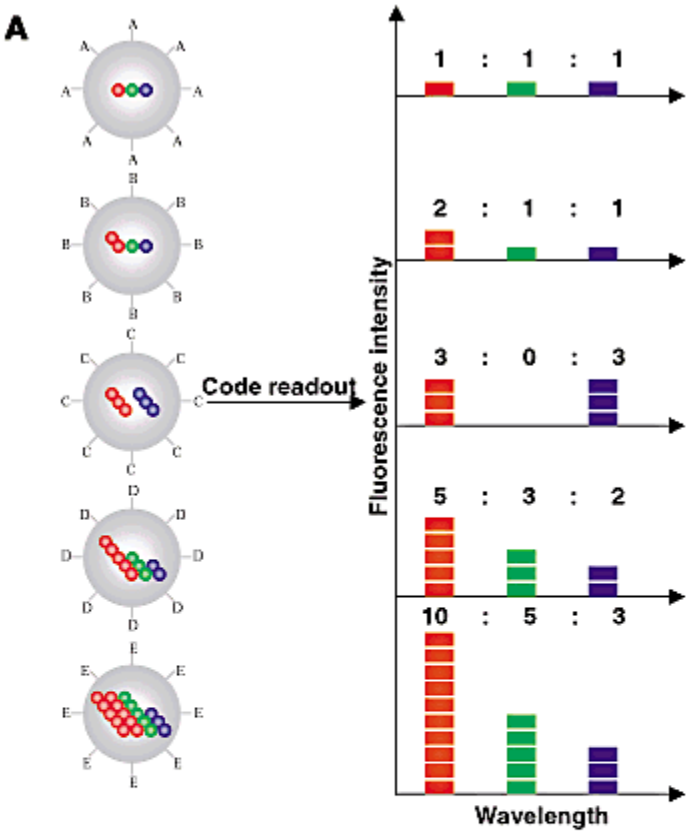
Robert Daniels
Chunming Niu

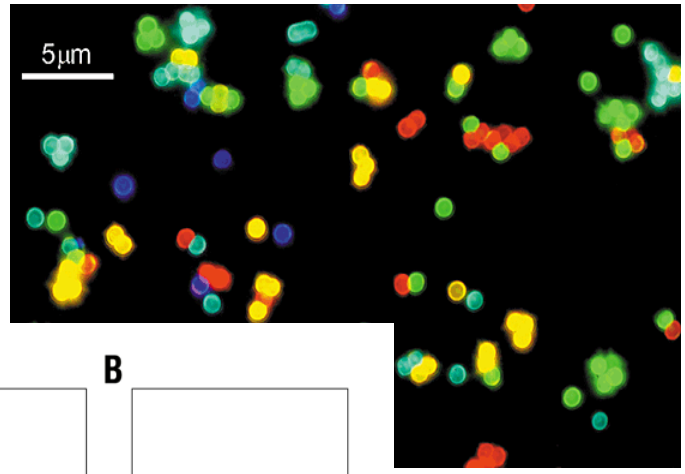
Nanoscale materials such as nanotubes and nanowires (20 nm diameter) can act as field effect transistors (FETs) at room temperature. NanoChemFET works because the conductive properties of nanowires are modulated by charges on the analyte molecule that act like a gate voltage in a conventional field effect transistor. Biosensors based on FETs would be sensitive, specific, and quantitative; they would not require complex instrumentation such as is typically used for fluorescence detection, and analytes need not be labeled. Two SBIR grants support development of FETs for detecting specific nucleic acid sequences and proteins.

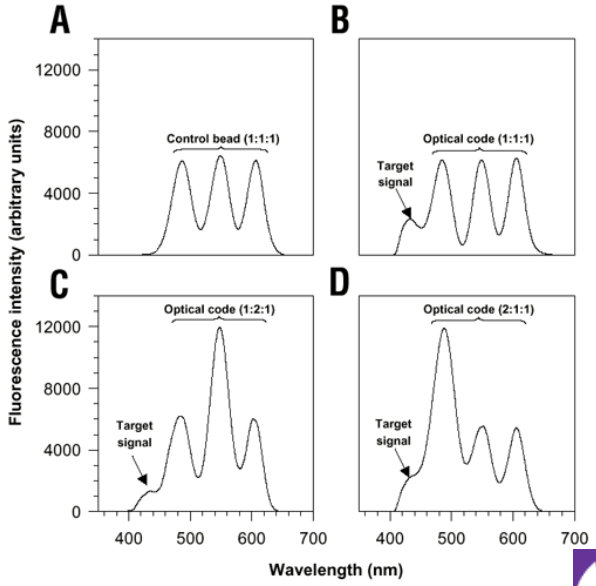
GEORGIA TECH

Department of Chemistry

Shuming Nie, Ph.D.

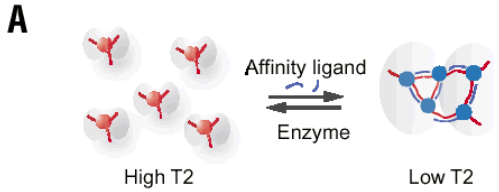


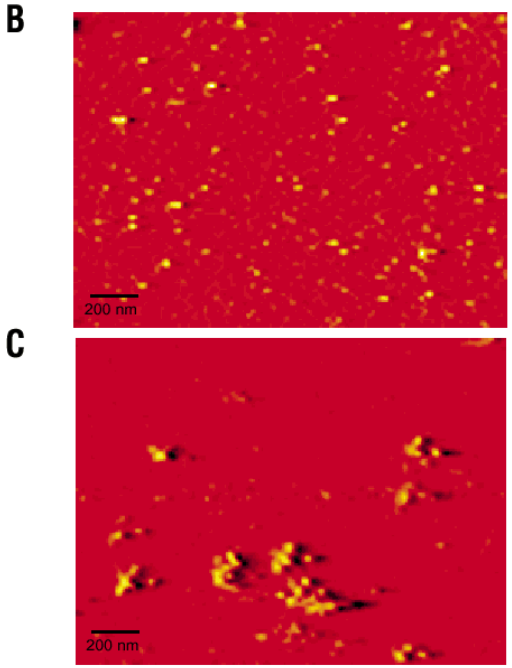




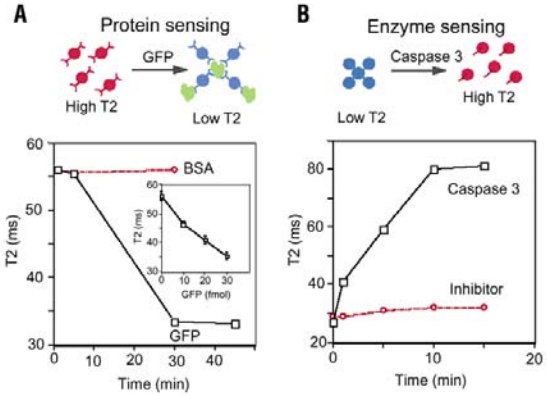
Nature Biotech., 2001, *19*:631-635

NIGMS



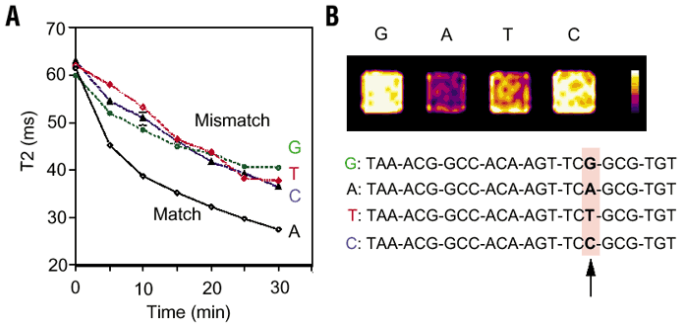


Nature Biotech., 2002, *20*:816-820



MASS. GENERAL HOSPITAL

Ralph Weissleder, M.D.



Molecular relaxation switches are being developed as probes of molecular interactions. Superparamagnetic nanoparticles assemble into complexes in the presence of binding targets, and complexes disassemble in the presence of enzymes. The signal may be detected by magnetic resonance imaging in turbid media and in whole-cell lysates, and may be useful for *in vivo* imaging.

PRINCETON UNIVERSITY

Edward C. Cox, Ph.D.

Robert Austin, Ph.D.

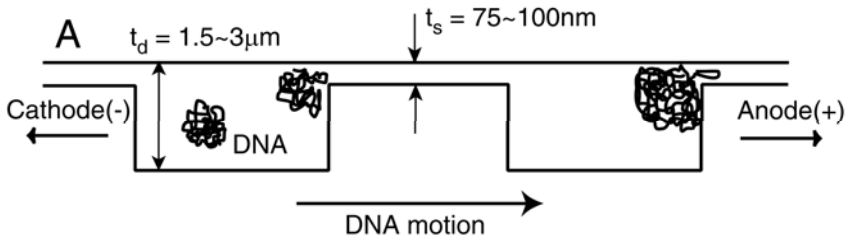
Princeton University

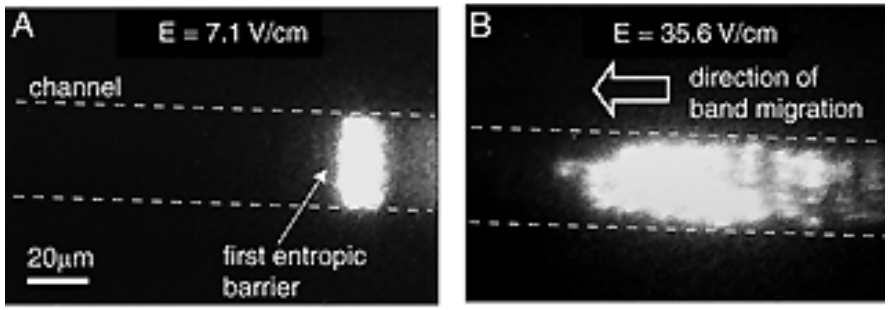
CORNELL UNIVERSITY

Harold G. Craighead, Ph.D.

CORNELL UNIVERSITY

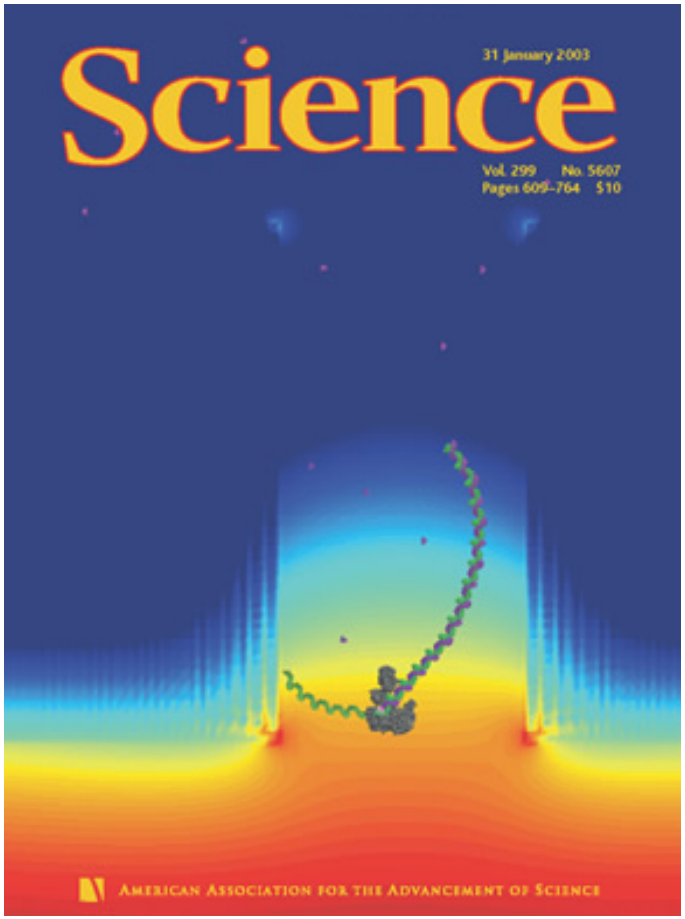
Structures nanofabricated in silicon may replace polymers in devices for DNA analysis. In this experiment, DNA molecules are trapped in deep entropic traps until a portion of the molecule stretches so that it can enter the shallow space, and then the rest of the molecule follows. DNA separations that would ordinarily take 12-24 hours took only 15-30 minutes. Similar systems could be used to analyze other kinds of molecules.





Science, 2001, *288*:1026-1029

NATIONAL HUMAN GENOME RESEARCH INSTITUTE



CORNELL UNIVERSITY

Watt W. Webb, Sc.D.

Harold G. Craighead, Ph.D.

A single molecule of DNA polymerase is immobilized inside a zero-mode waveguide. DNA synthesis is followed in real time by observing fluorescence bursts from labeled nucleotide analogs as they are incorporated into the growing DNA strand.

Efficient DNA synthesis occurs only at substrate concentrations much higher than the pico- or nanomolar regime typically required for single molecule analysis. Zero-mode waveguide nanostructures have been developed to overcome this limitation. They effectively reduce the observation volume to tens of zeptoliters, thereby enabling the observation of the single fluorescently labeled substrate molecule present within the guide, at the location of the molecular event, in a background of micromolar concentration of fluorescently labeled substrate molecules diffusing throughout the solution but outside of the observation volume.

M.J. Levene, et al., Science, 2001, *299*: 682-686.

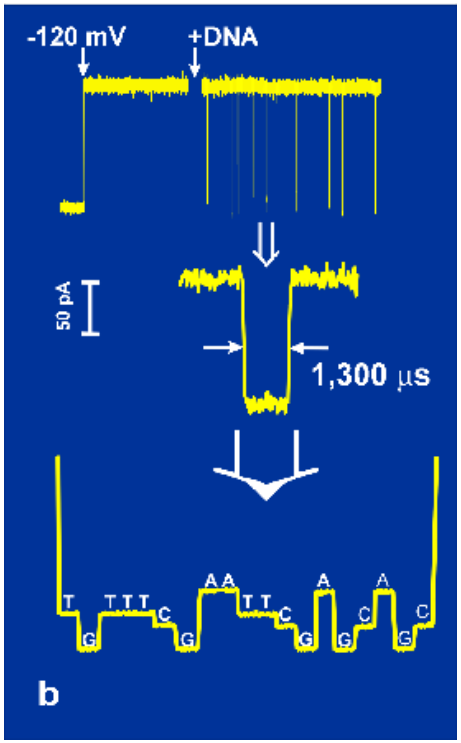
UNIV. OF CALIFORNIA SANTA CRUZ

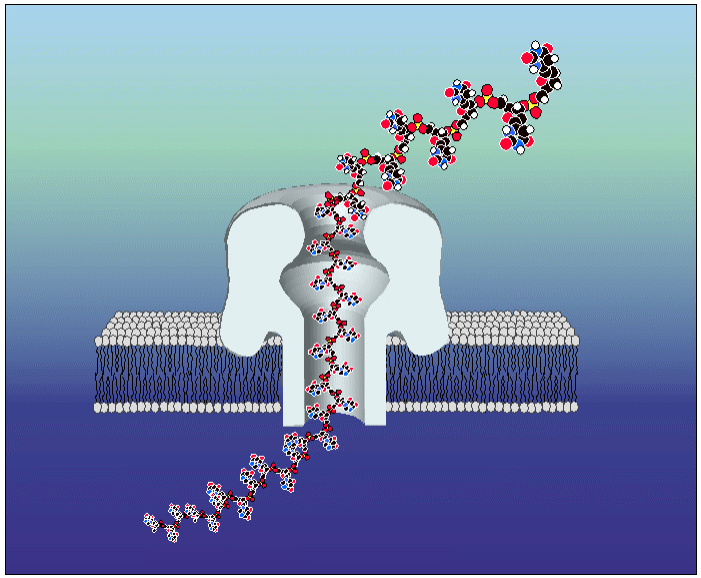
Department of Chemistry & Biochemistry

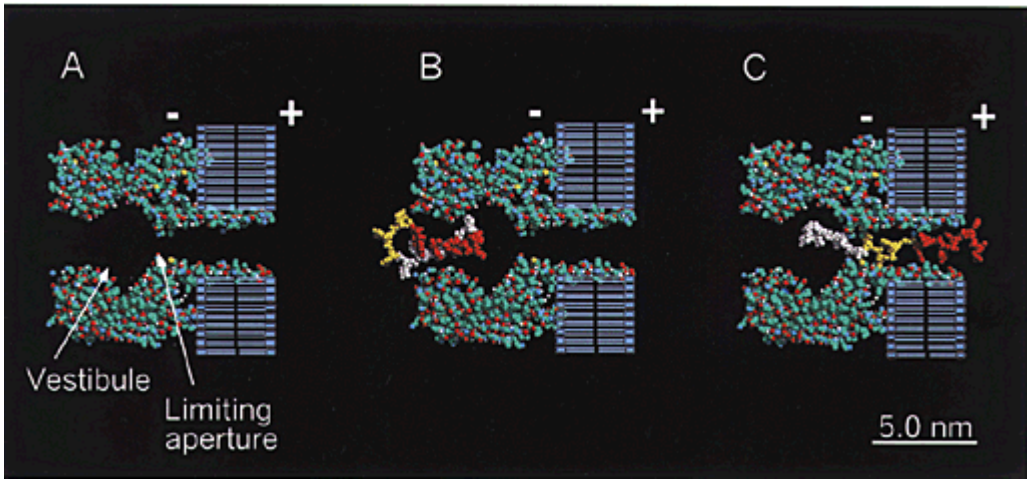
David W. Deamer, Ph.D.

UC SANTA CRUZ

Single-stranded nucleic acid molecules passing through a nanometer-sized pore modulate the ionic conductance across the membrane. This observation may one day lead to a device for single molecule DNA sequencing.





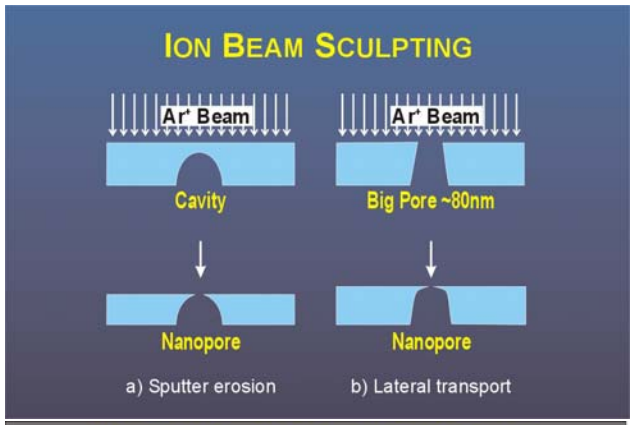


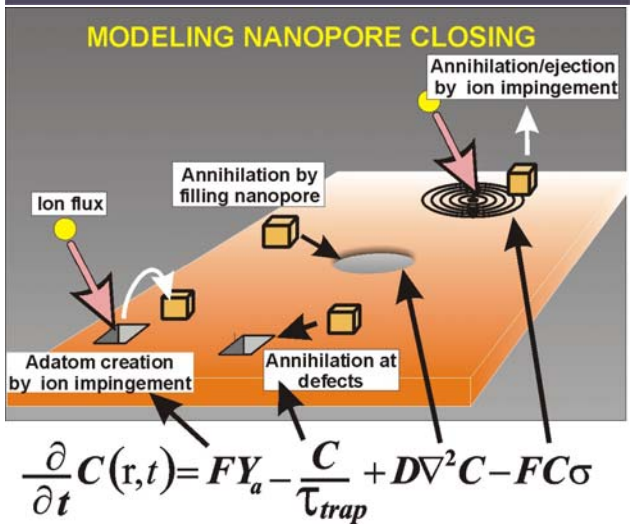
NATIONAL HUMAN GENOME RESEARCH INSTITUTE

HARVARD UNIVERSITY

Dept. of Mol. and Cellular Biology
Daniel Branton, Ph.D.

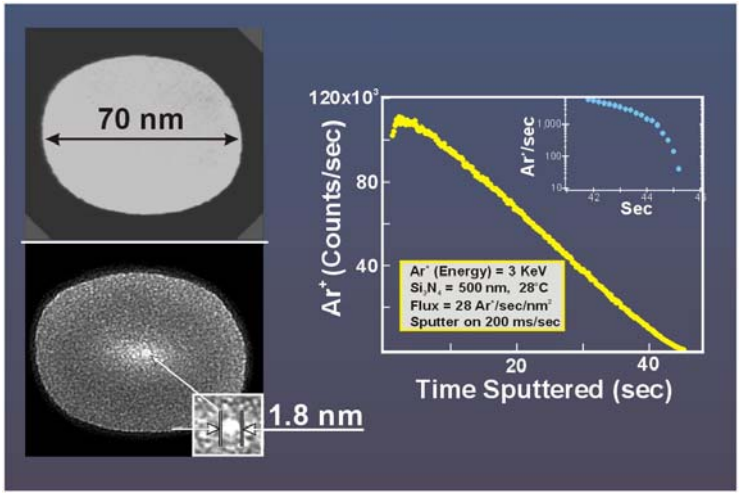
Dept. of Physics
Jene A. Golovchenko, Ph.D.





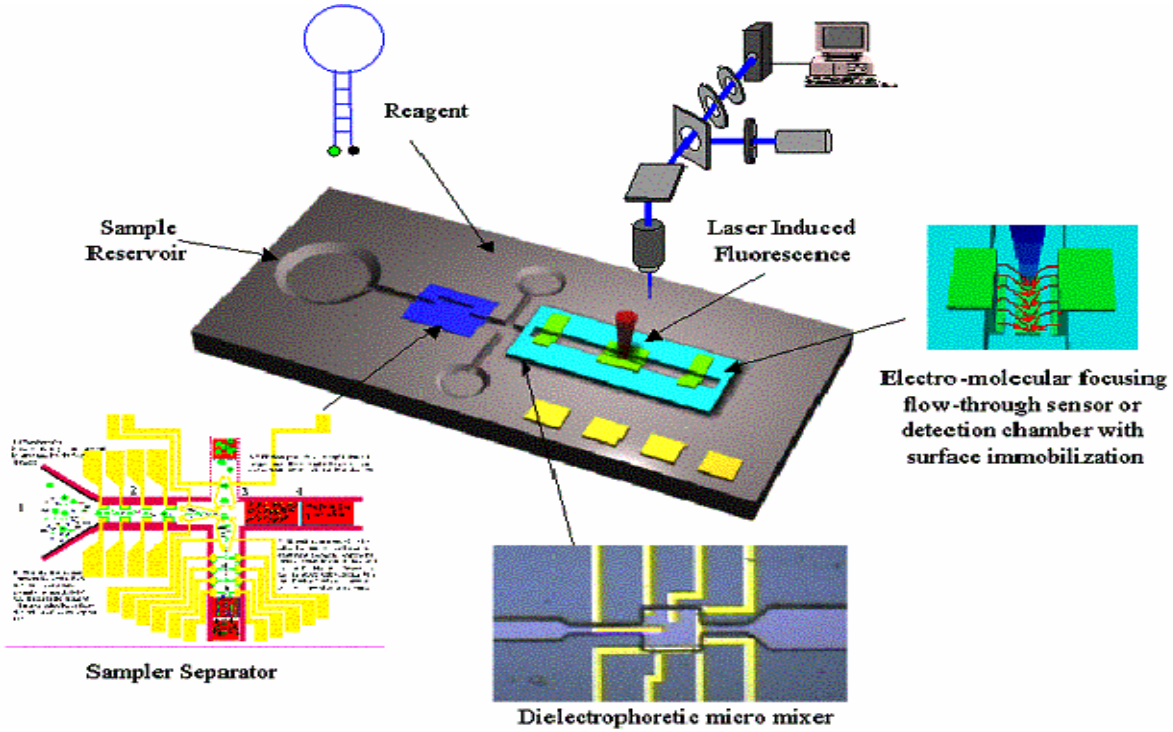
Nature 2001 *412:*166-169

Solid state fabrication methods were developed to create a pore small enough for single-stranded DNA analysis. An incident beam of massive argon ions closes a pre-made hole. Size control is achieved by monitoring ion flux through the pore. The result is a "robust electronic detector consisting of a single nanopore in a Si_3N_4 membrane, capable of registering single DNA molecules in aqueous solution."



DARPA
NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Integrated multifunctional systems.



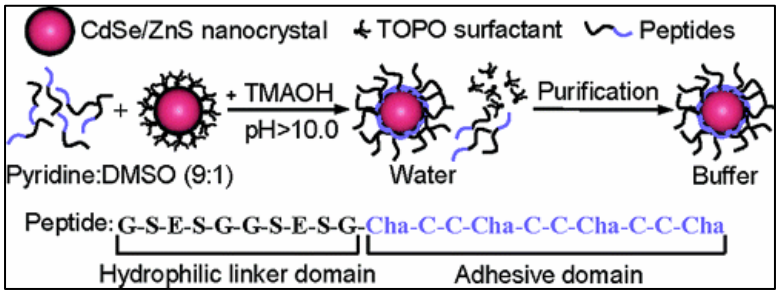
The detection chip includes: i) a chamber inlet where saliva is introduced; ii) phase shifted electric fields that enable traveling wave dielectrophoresis which focuses the stream of cells in the microfluidic flow channel for subsequent separation; iii) flow with specific amplitudes and frequencies of the AC electric field for the separation of cell from proteins; and iv) the detection chamber that includes the different ligands for simultaneous optical detection of multiple analytes. Illustration by Drs. David Wong and Chih-Ming Ho. UCLA

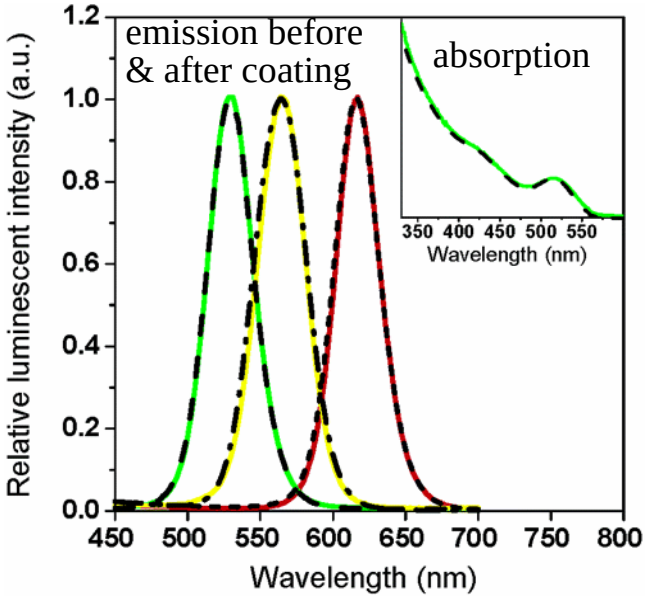
Imaging

UNIV OF CALIFORNIA, LOS ANGELES

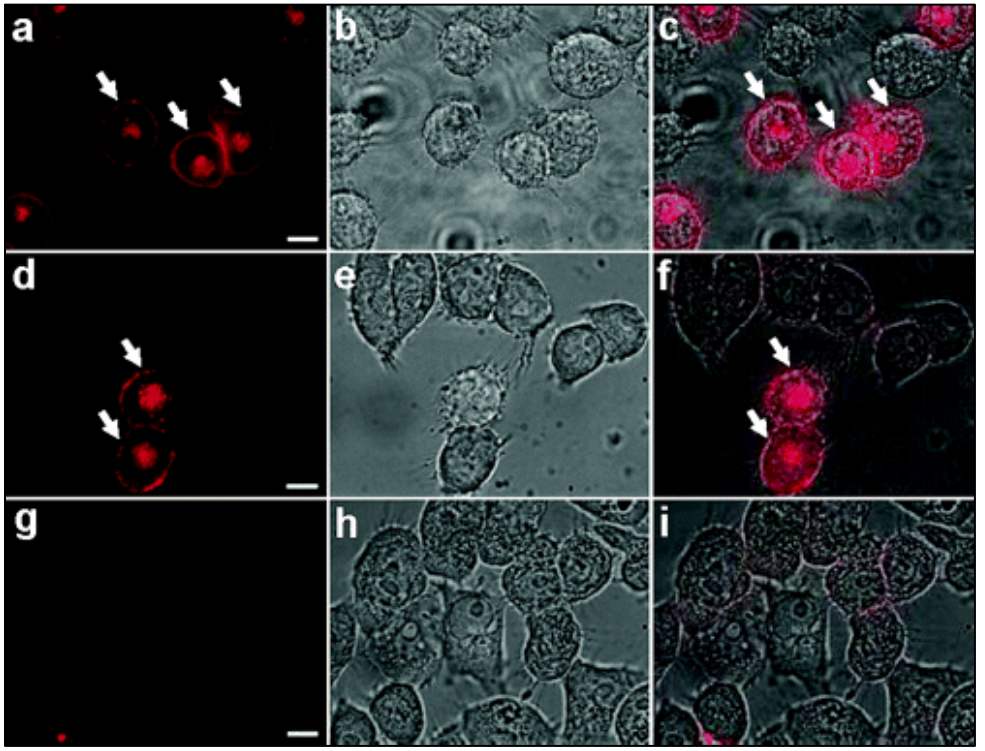
Chemistry and Biochemistry

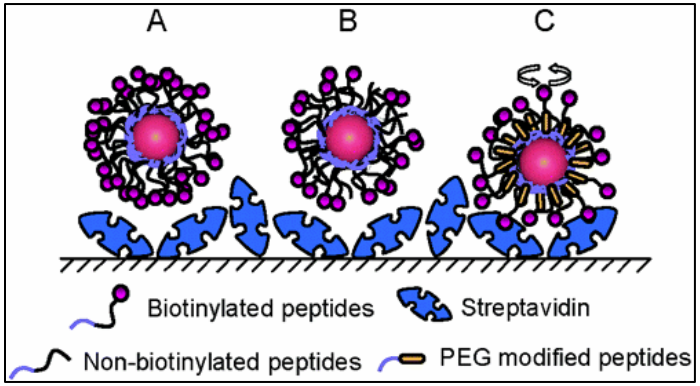
Shimon Weiss, Ph.D.



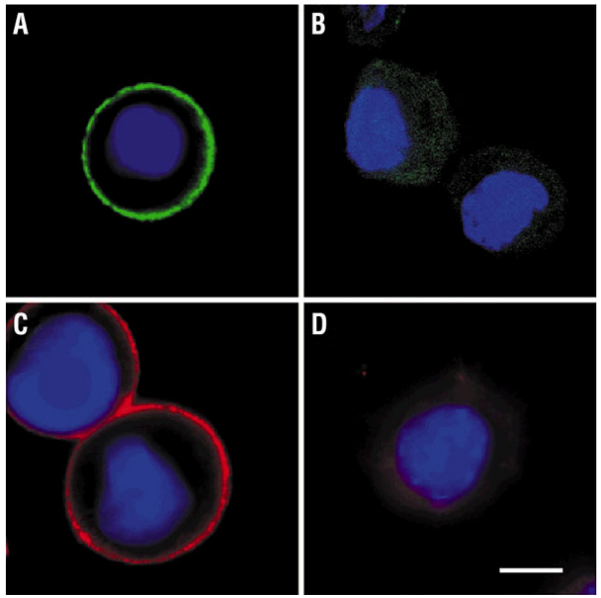


F Pinaud, et al., J. Am. Chem. Soc., 2004,
ASAP Article Web Release Date: April 22, 2004

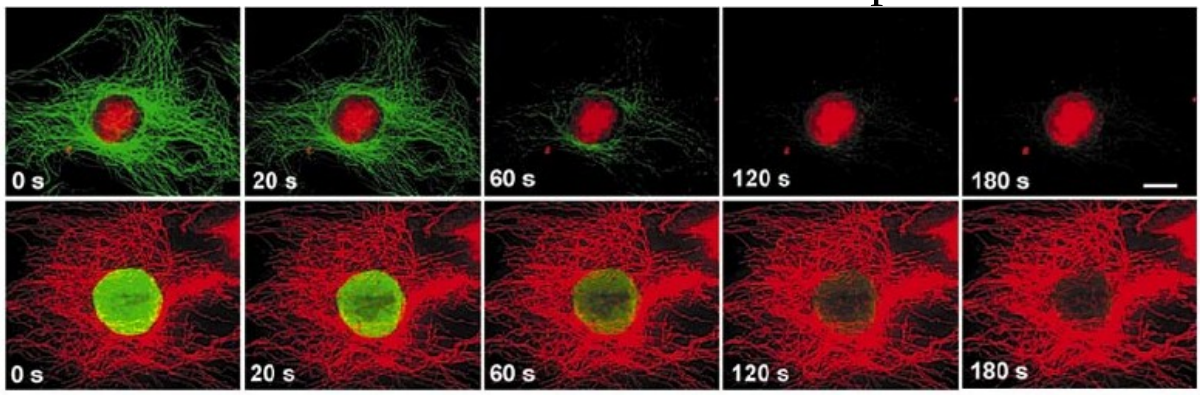




BRP



Nature Biotech., 2003, *21*:41-46



QUANTUM DOT CORP.

Marcel Bruchez, Ph.D.

Semiconductor quantum dots are being developed for use as probes for intracellular structures. In this study, they were used to label the breast cancer marker Her2 on the surface of fixed and live cancer cells, to stain actin and microtubule fibers in the cytoplasm, and to detect nuclear antigens inside the nucleus. Quantum dots offer several advantages over the organic dyes typically used for comparable studies.

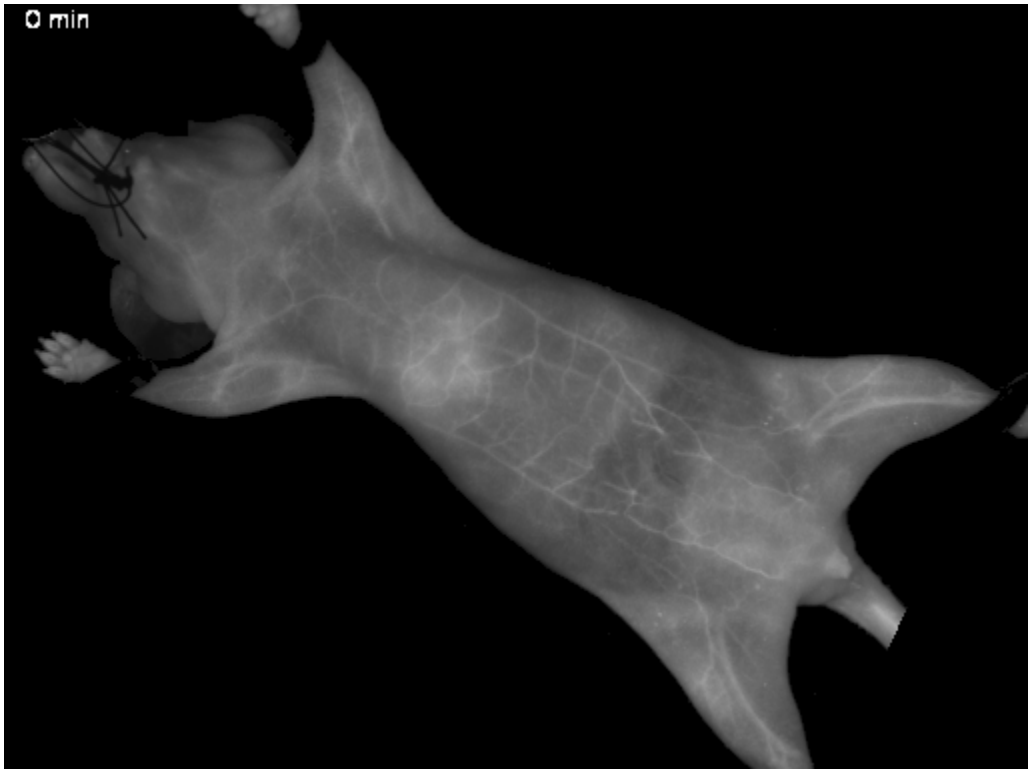
QUANTUM DOT

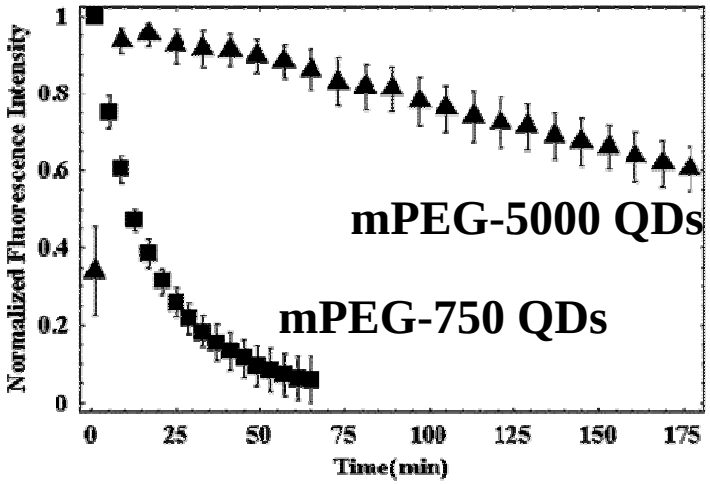
NATIONAL CANCER INSTITUTE

CARNEGIE-MELLON UNIVERSITY

Molecular Biosensor and Imaging Center

Alan S. Waggoner, Ph.D.





circulating lifetime of QDs

B. Ballou, et al., Bioconjugate Chem., 2004, *15*:79 -86

Timelapse: Mouse injected with methoxy-PEG750-Qdots

QUANTUMDOT

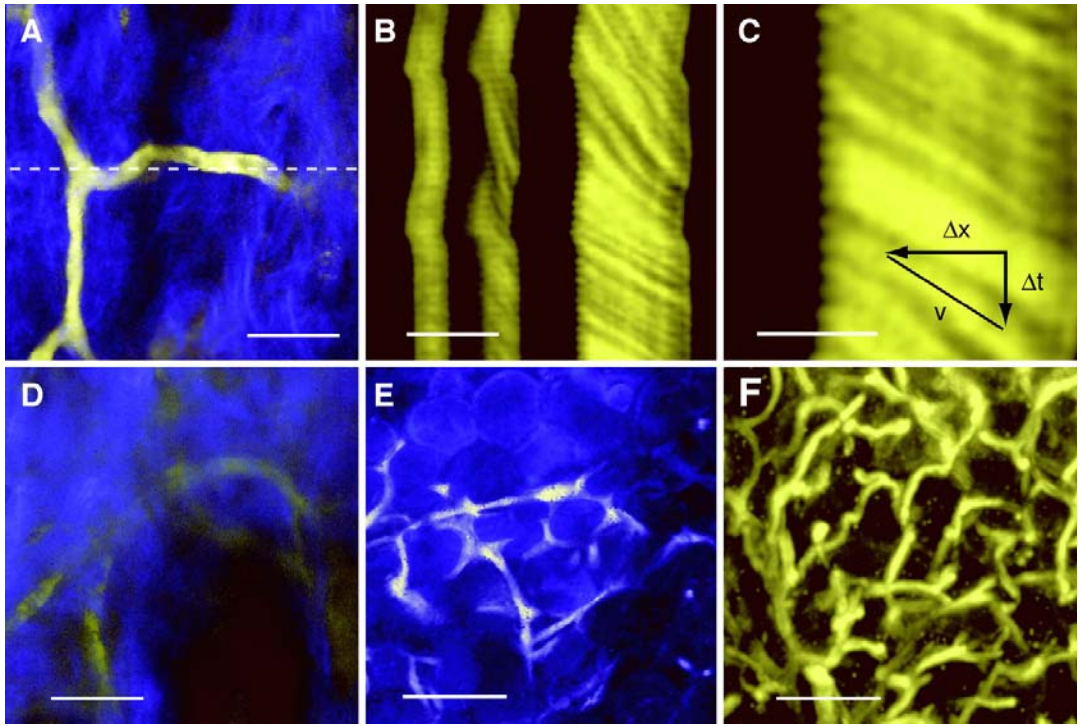
Carnegie Mellon

BRP

NIBIB

CORNELL UNIVERSITY
Watt W. Webb, Sc.D.

QUANTUM DOT CORP.
Marcel Bruchez, Ph.D.



D.R. Larson, D.R.et al., Science, 2003, *300*:1434-1436.

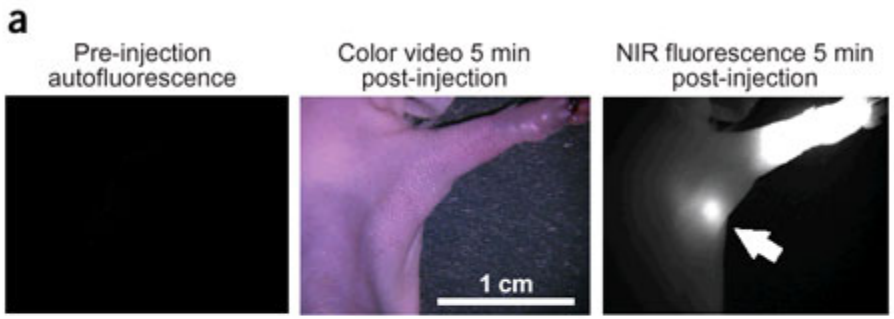
Semiconductor quantum dots were imaged by multiphoton microscopy through the skin of living mice. Blood flow velocity and heart rate (from undulation of the capillary wall) could be determined through the skin.

No adverse effect on the mice was observed (the mice are being maintained to investigate long-term Qdot toxicity).

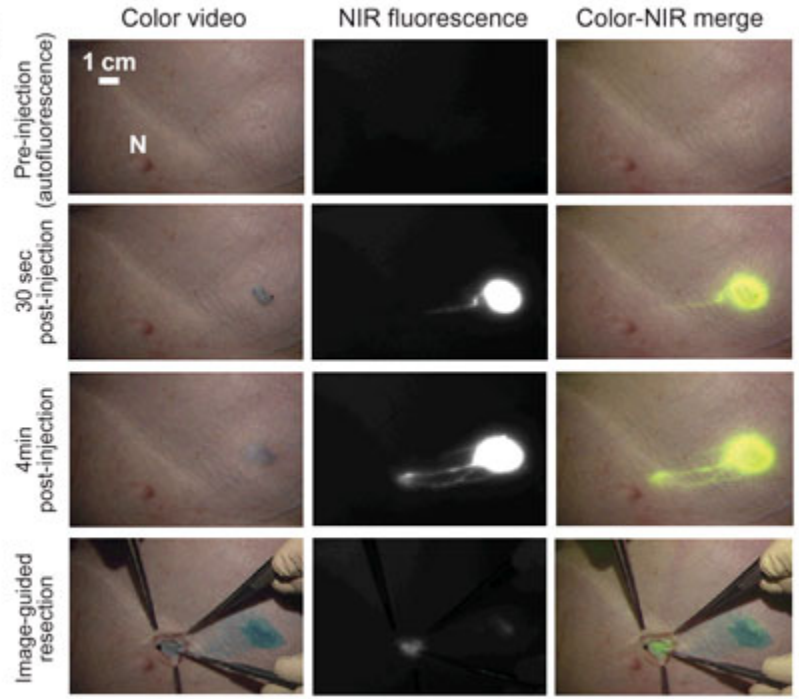
National Center For Research Resources
National Cancer Institute

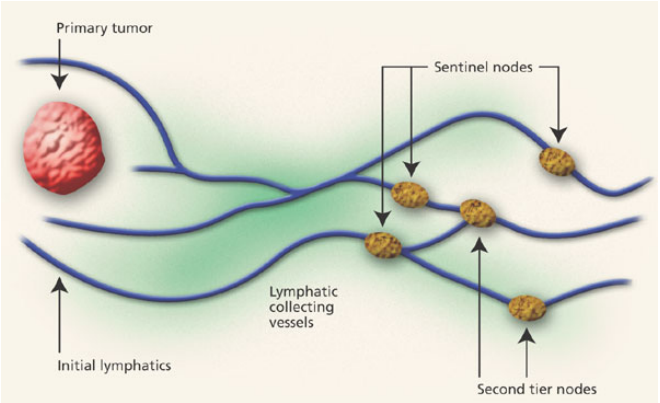
MIT
Moungi G. Bawendi

Beth Israel Deaconess Medical Center
John V. Frangioni



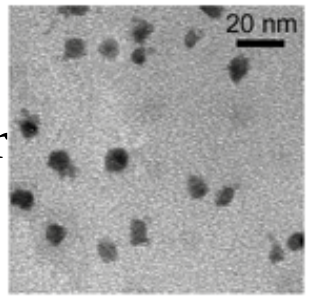
S. Kim, et al., Nature Biotech, 2004, *22*:93-97





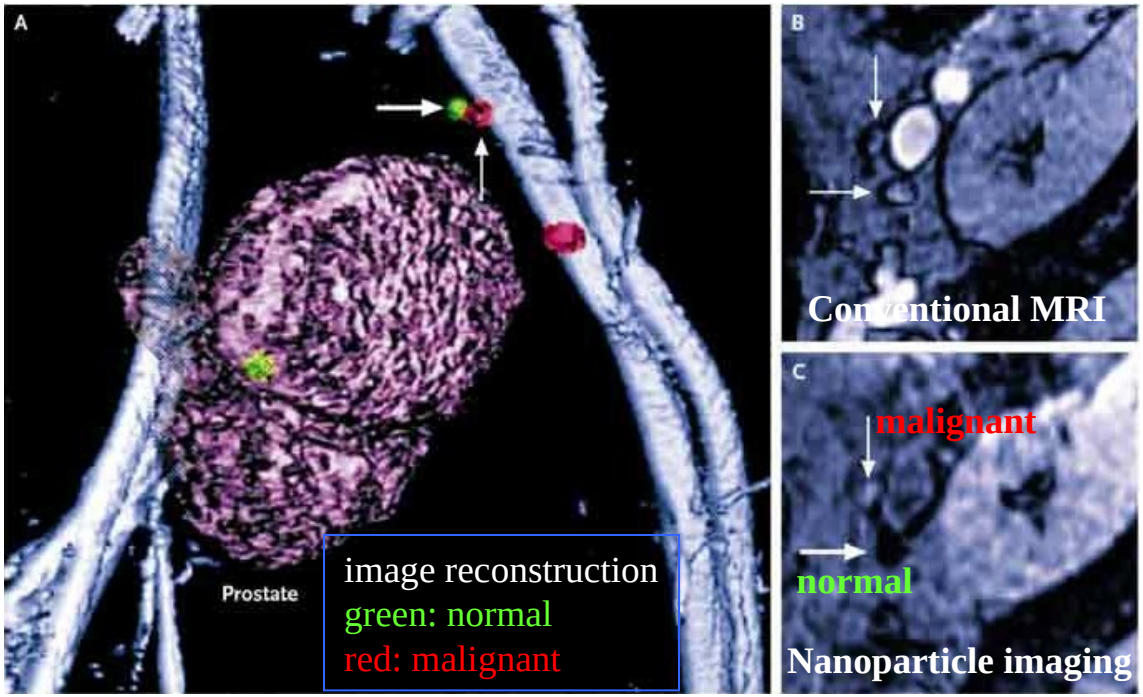
R. Uren, Nature Biotech., 2004, *22*:38-39

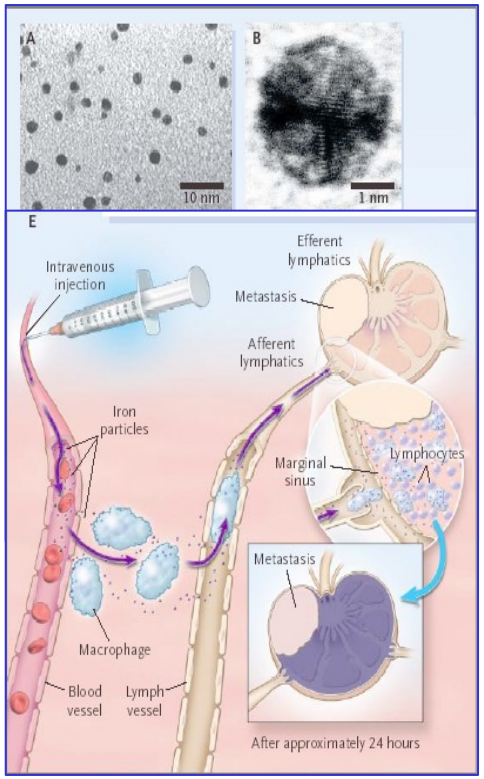
Following intradermal injection of 10-20 nm phosphine coated (water soluble) near IR fluorescent quantum dots into the paw of a mouse or thigh of a pig, lymph nodes 1 cm deep are imaged in real time using low intensity illumination, enabling sentinel lymph node biopsy under image guidance.



Mass. General Hosp.
Harvard Med. School
Ralph Weissleder

University Medical Center
the Netherlands
Jean de la Rosette





M.G. Harisinghani, et al.,
NEJM, 2003, *348:*2491-2499

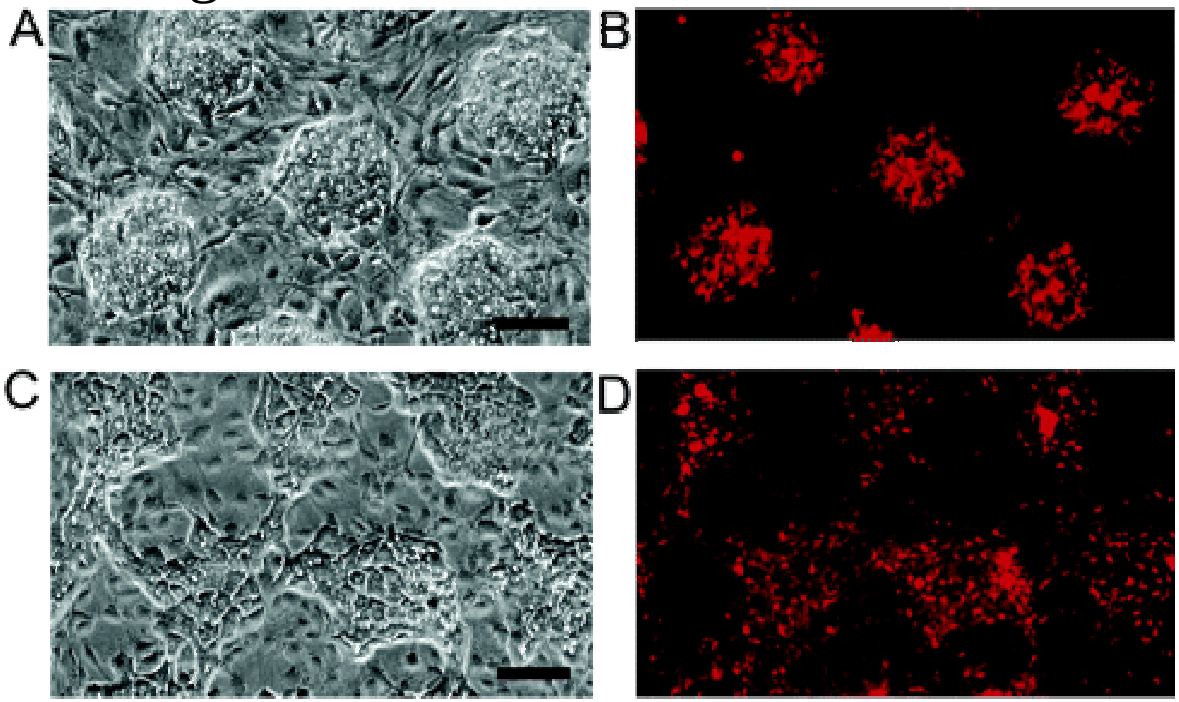
Nanoparticles (dextran-coated iron oxide crystals – Combidex, Advanced Magnetics) injected into the circulation travel to the lymph nodes. Metastatic tumors growing in the nodes interfere with particle distribution, and this can be detected by MRI. 80 men undergoing surgery or biopsy for prostate cancer had MRI exams both with and without the nanoparticles before surgery. 33 of the men actually had metastatic lymph nodes. MRI with the particles identified all 33, whereas MRI without the particles missed more than half of them.

NATIONAL CANCER INSTITUTE

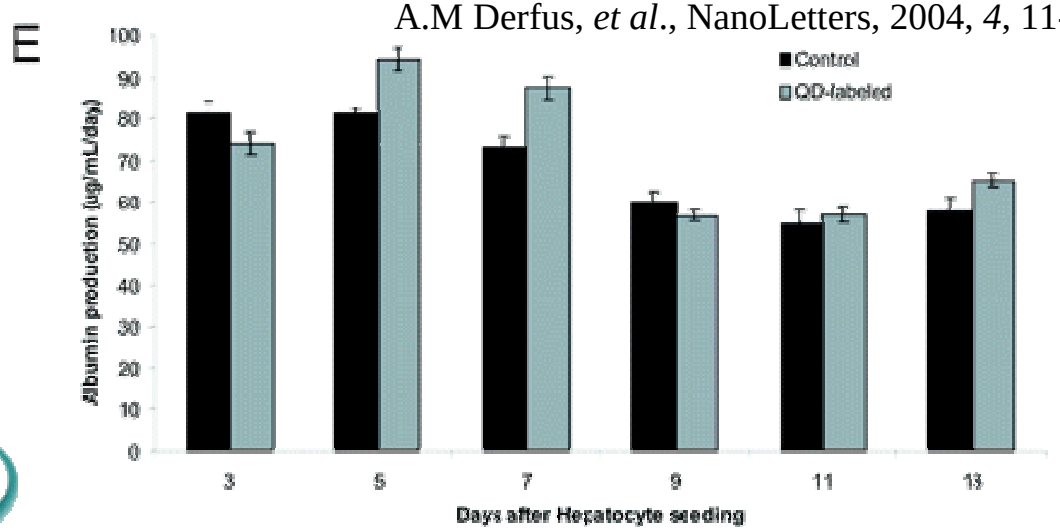
UNIV OF CALIFORNIA SAN DIEGO

Sangeeta Bhatia, Ph.D.

Liver is the site of cadmium toxicity *in vivo*. Using primary liver cells as a model, CdSe-core quantum dots were acutely toxic under certain conditions. When appropriately coated, the quantum dots can be rendered nontoxic and used to track cell migration and reoganization *in vitro*. QDs were capped with ZnS, coated with PEG, and conjugated to EGF to promote uptake by hepatocytes. After 1 week, the hepatocytes co-cultured with fibroblasts changed shape and migrated as without QDs, and they produced normal levels of albumin for 2 weeks.

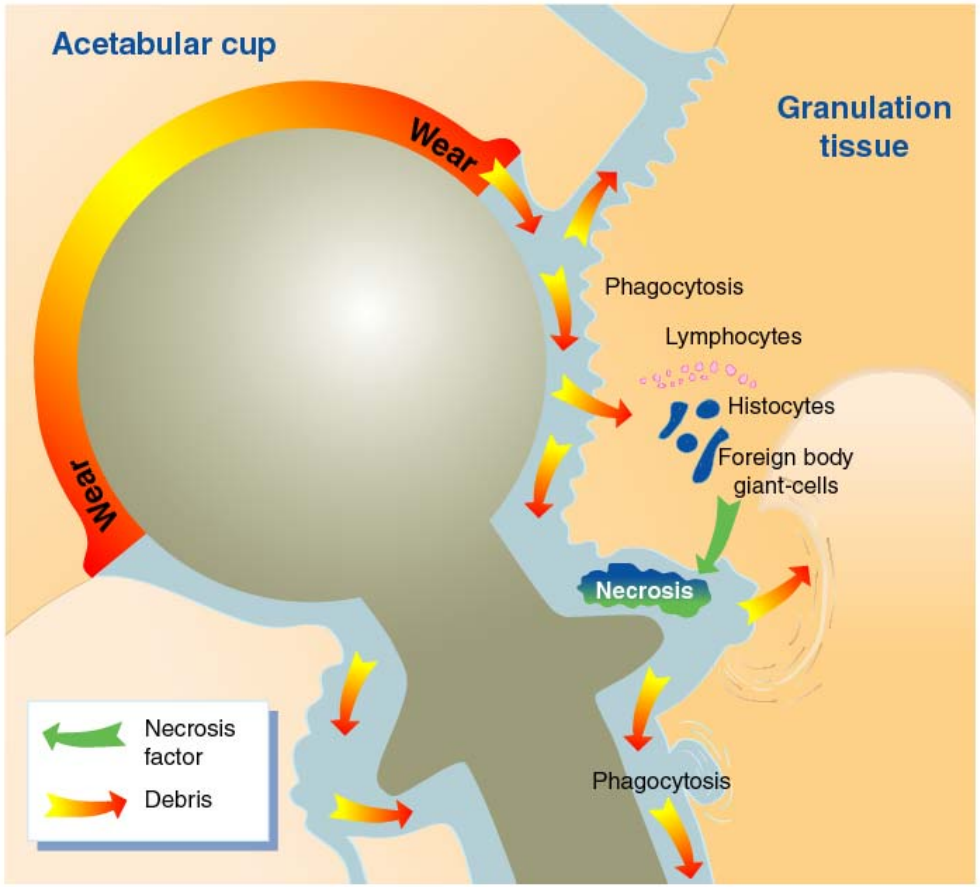


A.M Derfus, *et al*., NanoLetters, 2004, *4*, 11-18



Tissue Engineering

Total Hip Replacement - Osteolysis



We take about one million steps a year.

As years pass, strong shock waves caused by walking, running & climbing erode cushioning between ball & socket at top of leg.

Soon, bone grinding on bone causes osteoarthritis, a condition that brings crippling pain and slows everything we do.

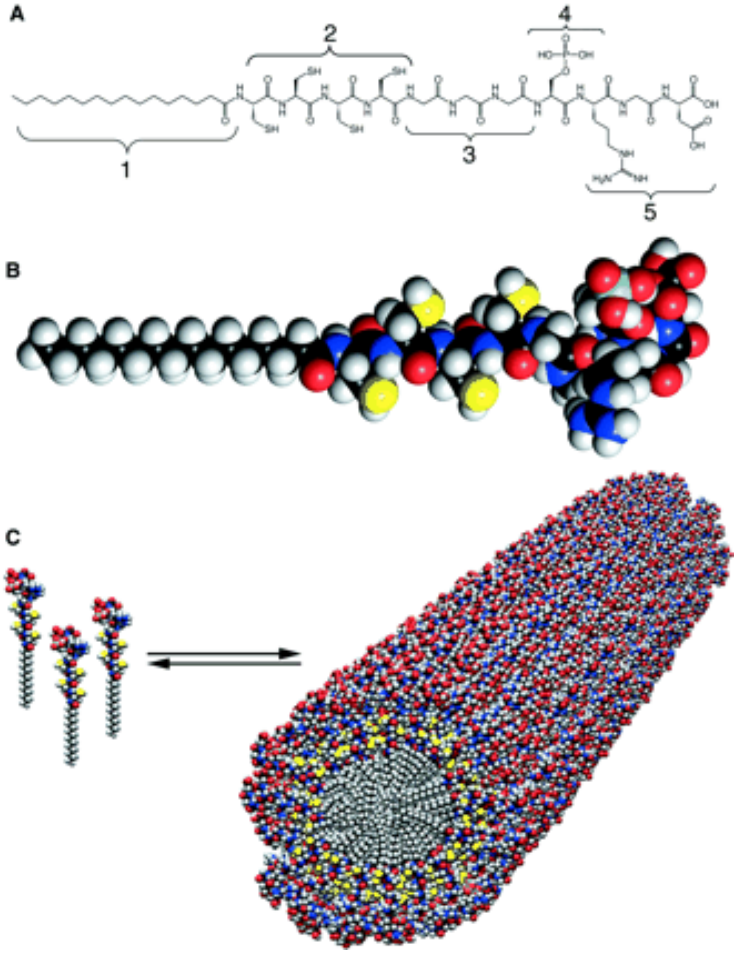
What's the answer? For more than 250,000 Americans a year: hip replacement surgery.

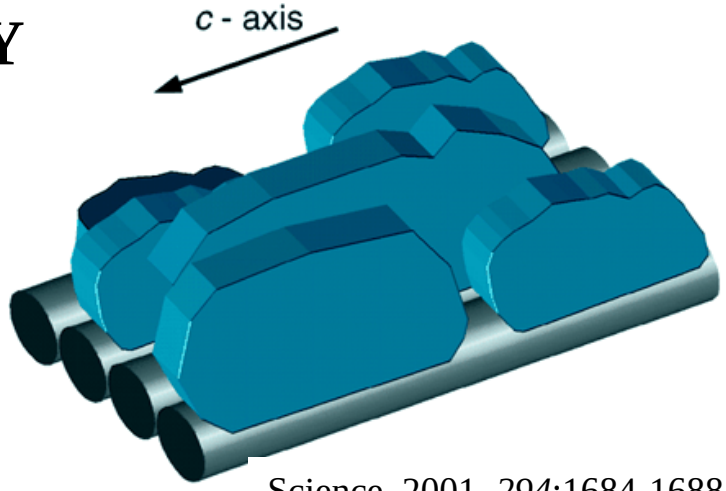
Provided by Dr. Tony Tomsia, Lawrence Berkeley National Laboratory (LBNL)

NORTHWESTERN UNIVERSITY

Samuel I. Stupp, Ph.D.

NORTHWESTERN UNIVERSITY



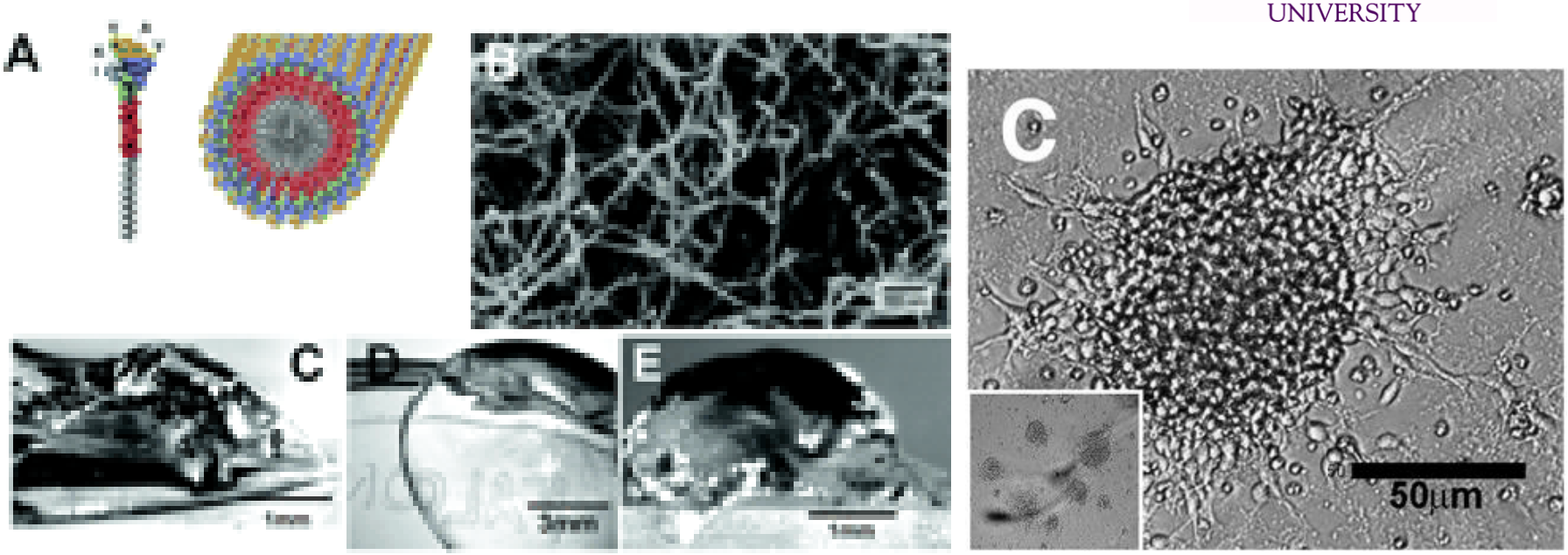


Science, 2001, *294*:1684-1688

pH-induced self-assembly of a peptide-amphiphile forms a nanostructured scaffold (micelle) reminiscent of extracellular matrix. The structural integrity of the nanofibers is controlled by reversible cross-linking. The alignment of crystals of hydroxyapatite, directed by the nanofibers, forms a composite material that mimics the alignment of hydroxyapatite on collagen fibrils in bone.

NORTHWESTERN UNIVERSITY

Samuel I. Stupp, Ph.D. & John A. Kessler, M.D.



pH-induced self-assembly of a peptide-amphiphile forms a nanostructured scaffold (micelle) reminiscent of extracellular matrix. The resulting three-dimensional scaffold presents the neurite-promoting laminin epitope IKVAV, and controls cell proliferation and differentiation. Neural progenitor cells encapsulated within the gel differentiate into neurons (see neurite extension) as opposed to astrocytes.

BRP
NINDS
NSF
NIBIB

Therapeutics

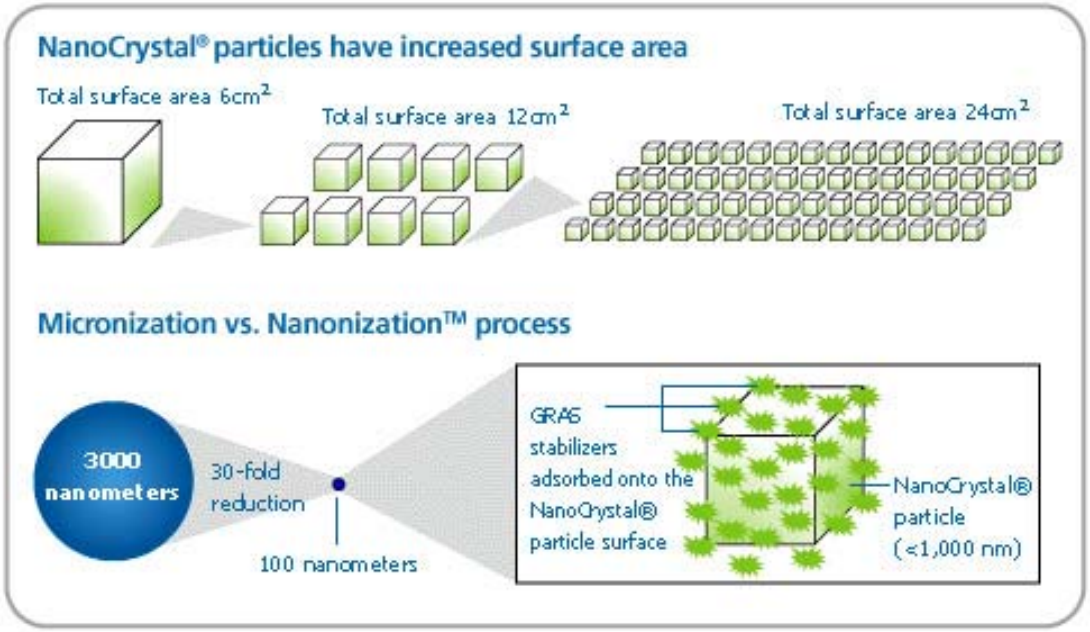
élan It's in everything we do

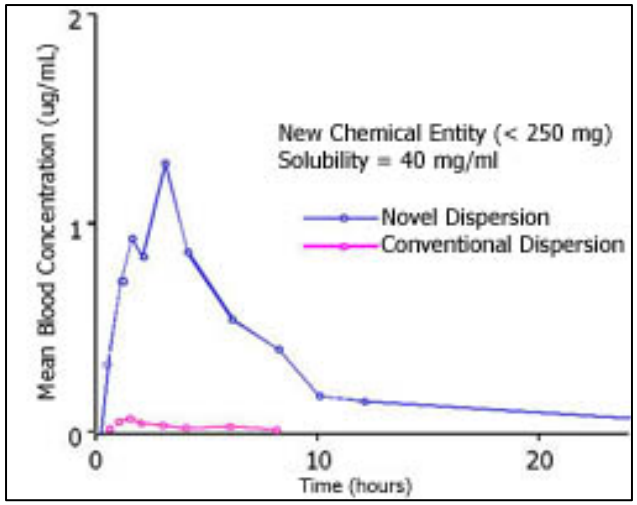
Increased surface area

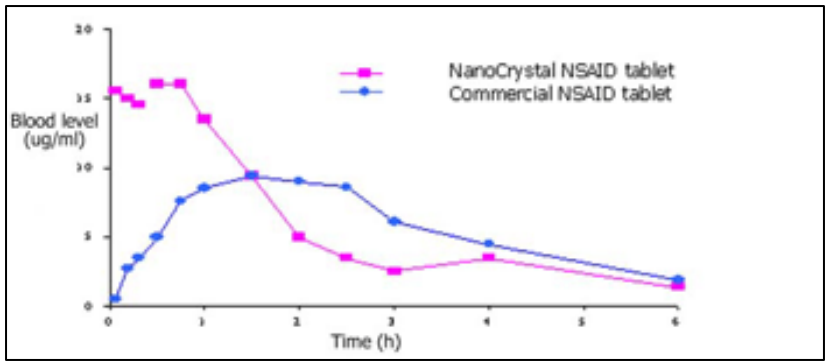
⇒ faster dissolution

⇒ faster absorption

⇒ enhanced bioavailability



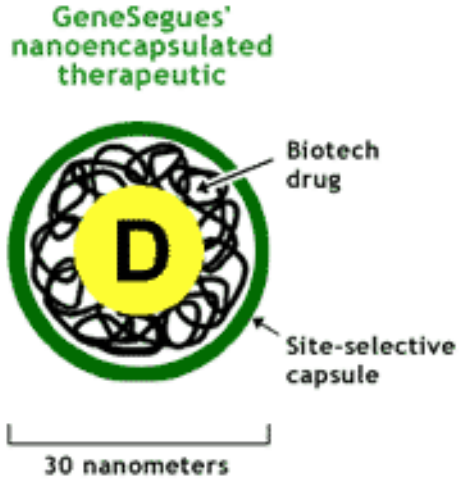




NANOCRYSTAL® TECHNOLOGY

Phase II clinical trial for nanocrystalline silver drug to treat inflammation and infection associated with atopic dermatitis. Unique form results in more rapid killing of bacteria and greater reduction in inflammation.

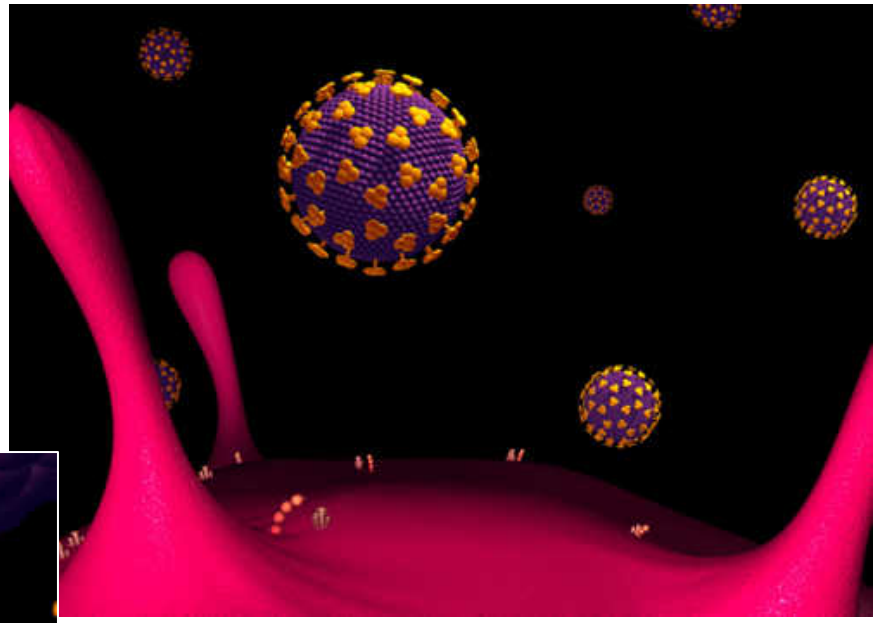
Phase II testing has been completed for use of Ferumoxytol, a nanoparticle iron oxide core surrounded by a carbohydrate coating, for iron replacement therapy, and phase II is ongoing for use as an intravascular blood pool agent that does not spread into the adjacent tissue, for MR angiography.

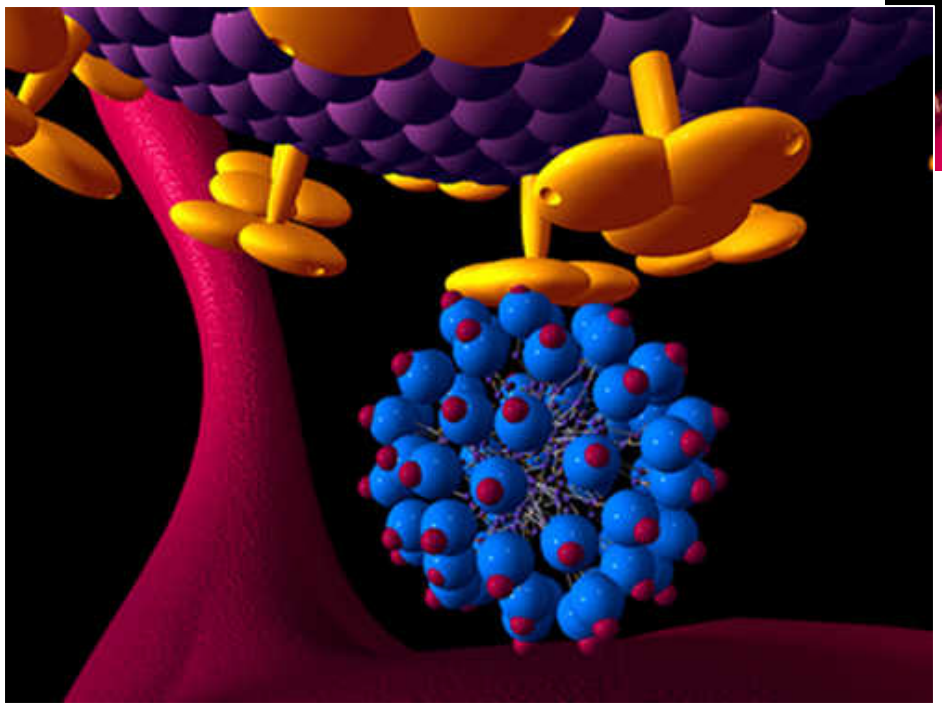


Preclinical testing of anti-cancer agent that delivers antisense oligos specifically to tumor cell nuclei through specific endocytic pathway.

STARPHARMA, LTD.
Thomas D. McCarthy

VivaGel is the first drug product based on dendrimers to enter human trials. It is a topical microbicide for prevention of HIV and other STDs.

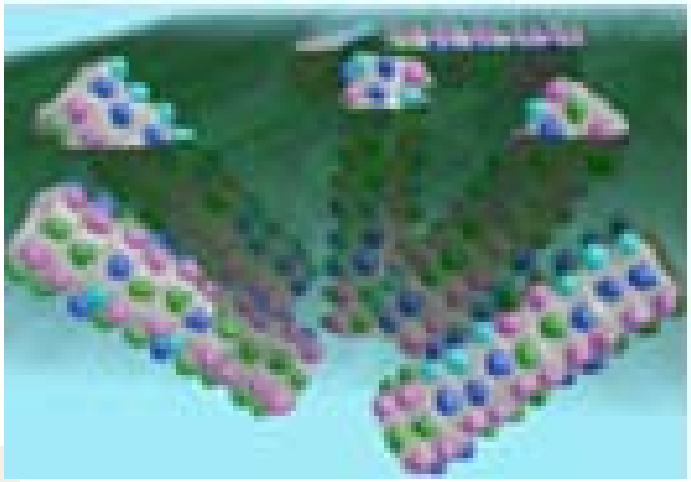


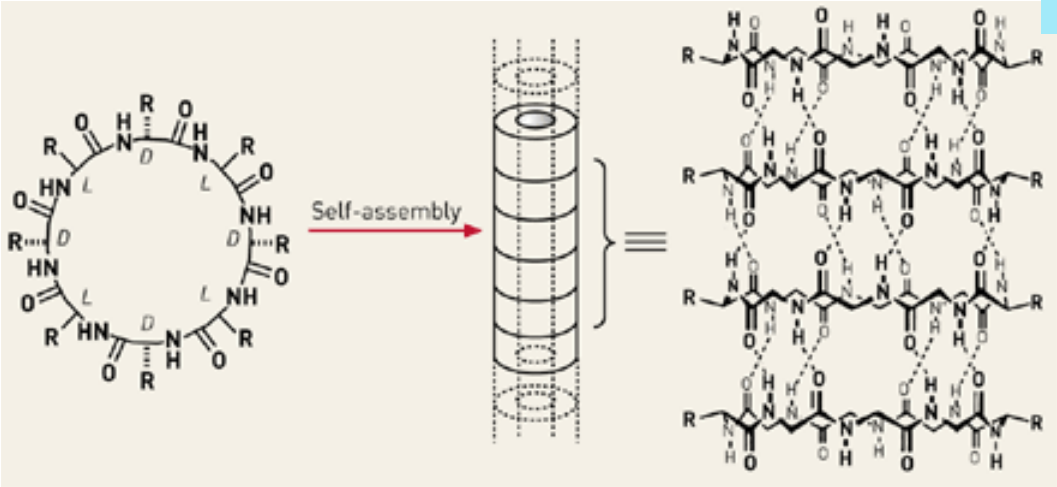


SCRIPPS RESEARCH INSTITUTE

M. Reza Ghadiri, Ph.D.

A new class of antibacterial peptides is being developed. Nanotubes are formed by self-assembly of cyclic peptides composed of alternating D- and L-amino acids. With appropriate design, the nanotubes insert themselves into bacterial, but not mammalian, cell membranes. Pores are created, resulting in bacterial cell death.

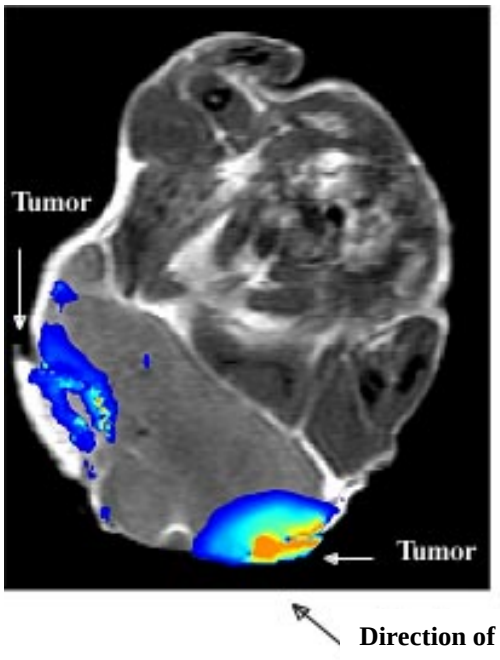


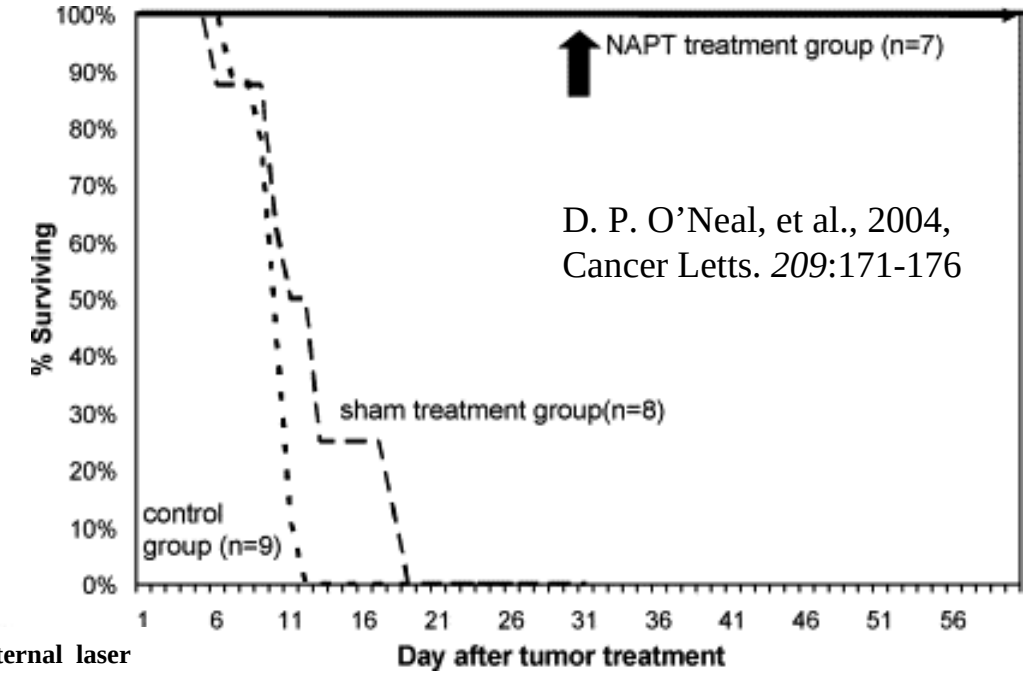


Figures are from C&E News, August 6, 2001

RICE UNIVERSITY; NANOSPECTRA BIOSCIENCES, INC.

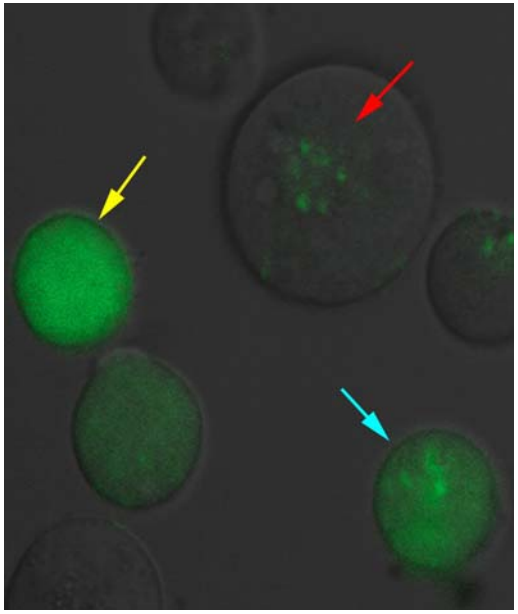
Jennifer L. West, Naomi J. Halas





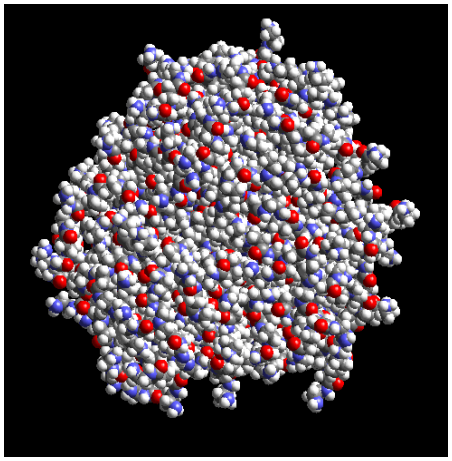
Tumor destruction by nanoparticle heating: nanoshells (110 nm silica core, 10 nm gold shell, PEG SAM) are tuned to absorb near-infrared light and emit heat, and to remain in the circulation of healthy animals. Upon injection into tail veins of mice, the particles leak out of the circulation and accumulate in tumors. NIR laser light was shined on the skin of the mice, near the tumors, resulting in heating of the tumors to 50°C, killing the tumors.
At 90 days the mice appeared healthy and tumor-free.

Integrated Devices

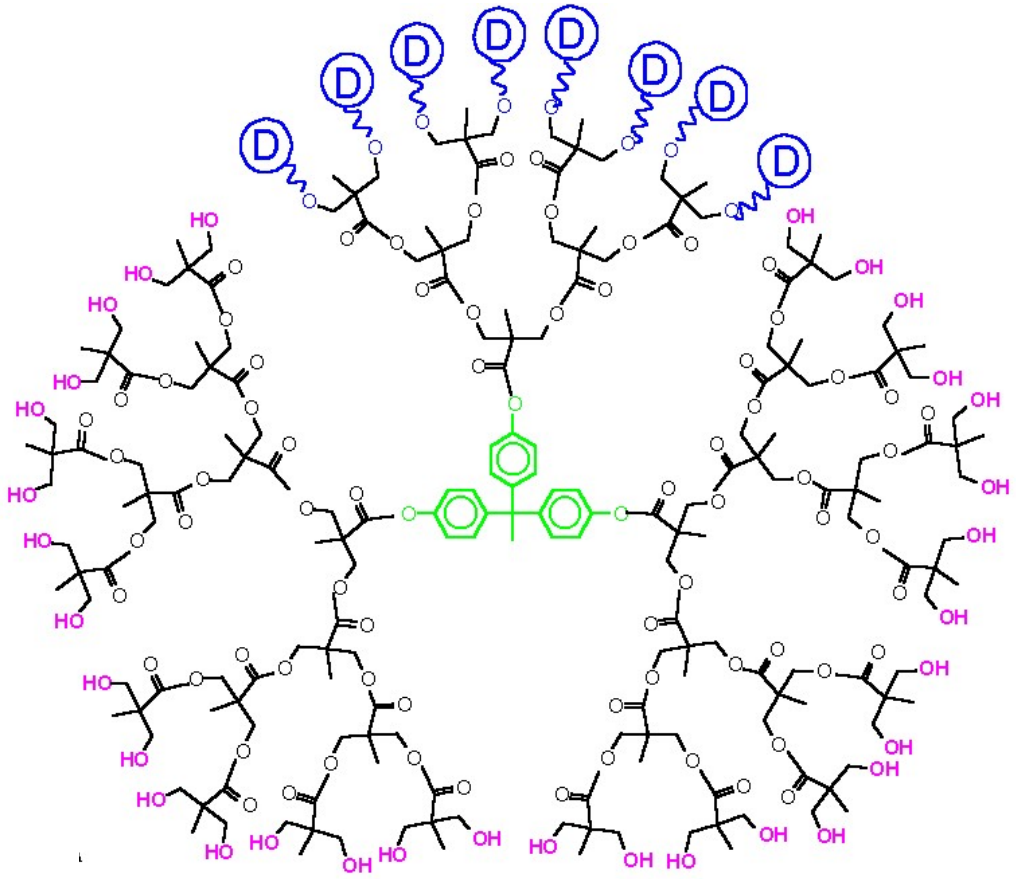


UNIVERSITY OF MICHIGAN

James Baker, M.D.



Multifunctional nano-devices based on dendritic polymer components will be developed that target neoplastic cells and sense the earliest signatures of cancer. The dendritic nano-devices will be designed to support the specific release of a therapeutic agent within a tumor, and analyze the effect of the therapeutic identifying evidence of residual disease.

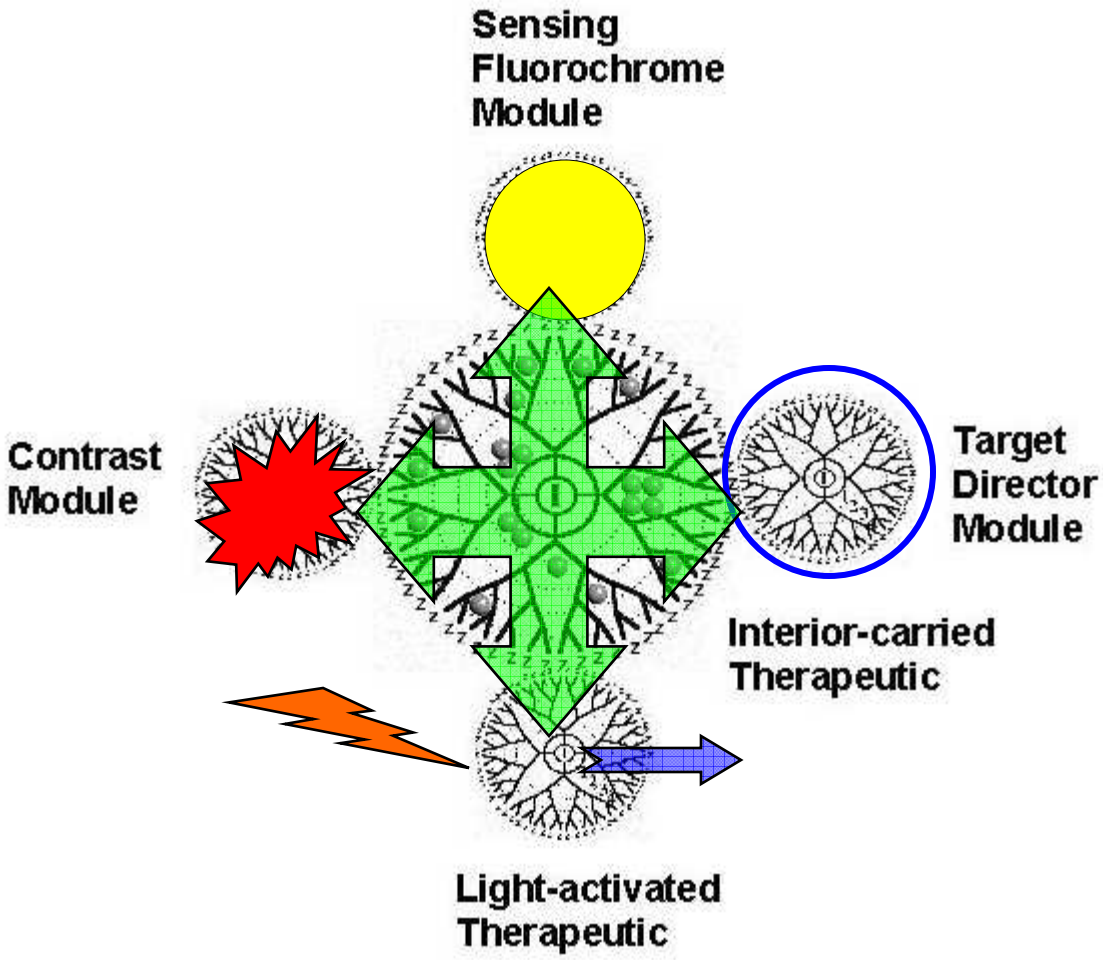


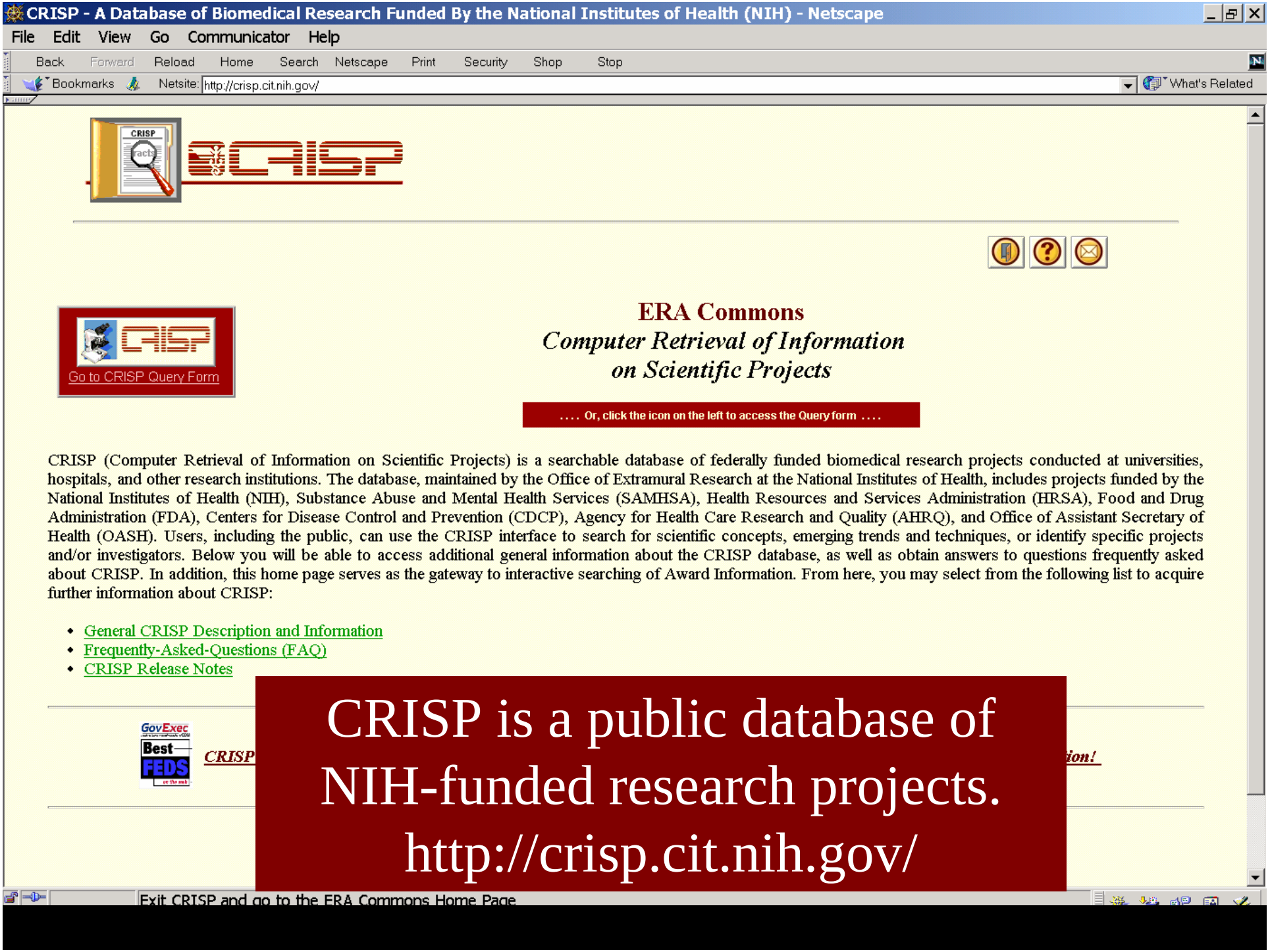
Dendrimer structure, from Jean Frechet, U.C. Berkeley

NIGMS

UNIVERSITY OF MICHIGAN

James Baker, M.D.

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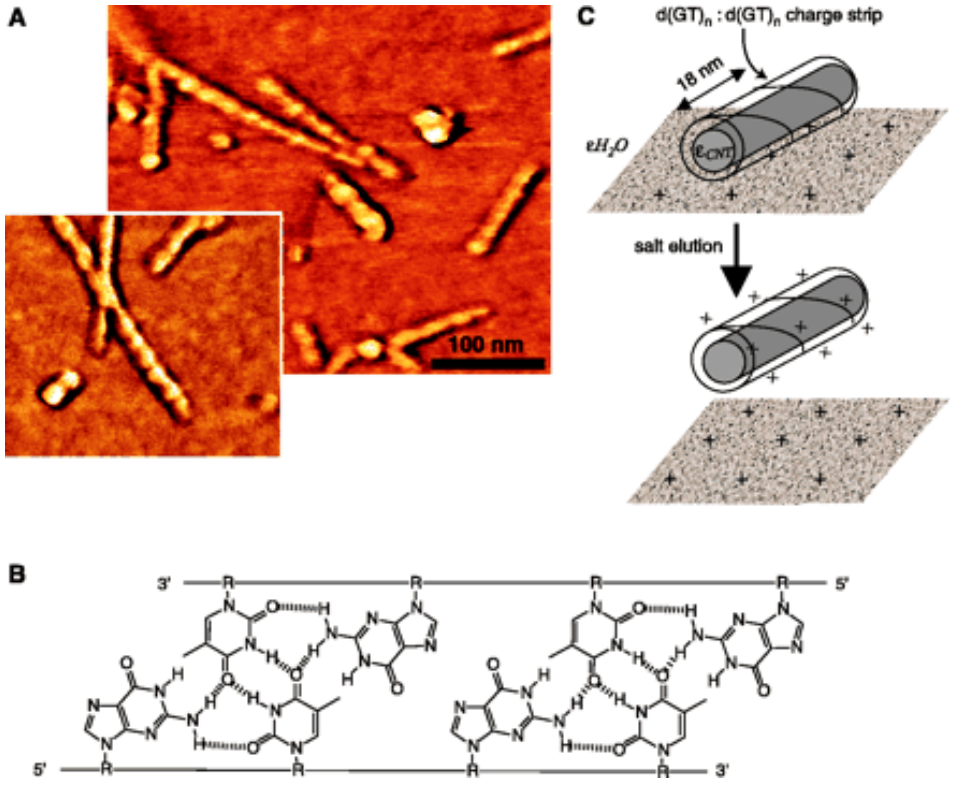
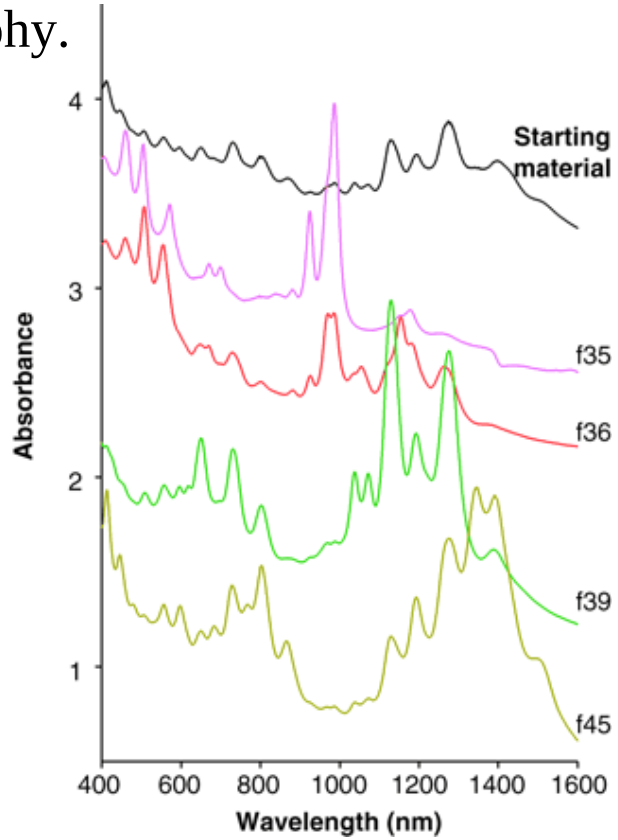
Biological knowledge informs other fields' nanotechnology advances.

DuPont	**MIT**	**UIUC**
Dennis J. Walls	Mildred S. Dresselhaus	Michael S. Strano

DNA forms a complex with carbon nanotubes, resulting in their dispersion in aqueous solution. d(GT)n, n=10-45, assembles around CNTs in a fashion that depends on tube diameter and electronic properties, enabling separation of different CNT structures by anion exchange chromatography.



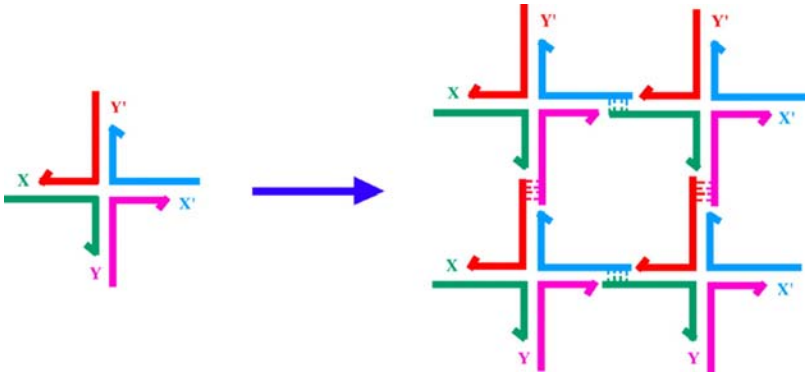
M.Zheng, et al., 2003, Science *302*:1545-1548.

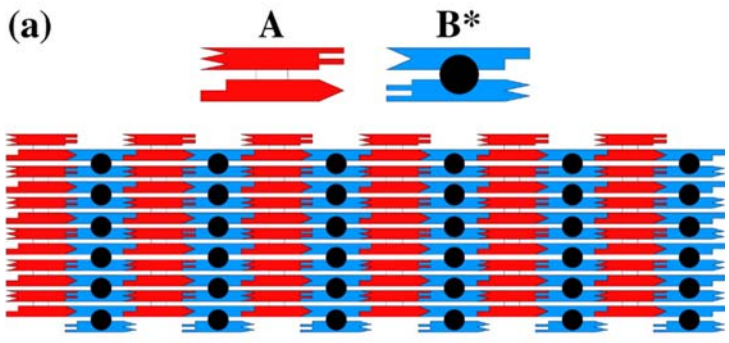


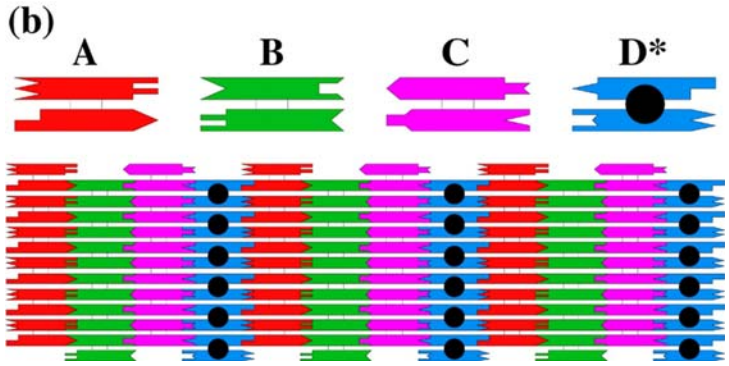
Earlier fractions (f35) contain smaller diameter & metallic CNTs while later fractions (f45) contain larger diameter & semiconducting CNTs.

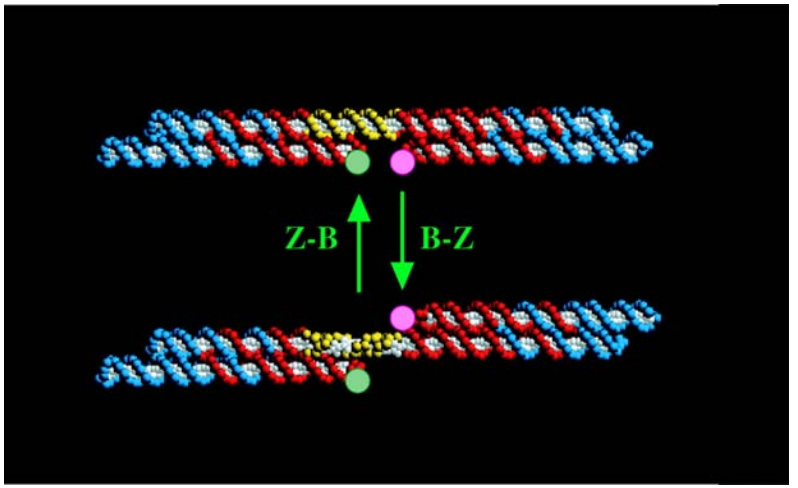
New York University

Nadrian C. Seeman









Complex devices may be built from the "bottom up" using a material called DNA. Nucleotide sequence determines the resulting structure (due to 'sticky ends' of high potential diversity), resulting in localization and interconnection of components. B* and D* contain modifications (hairpins) that protrude at right angles from the sheet, providing attachment points for subsequent assembly. Conformational changes can produce mechanical devices.

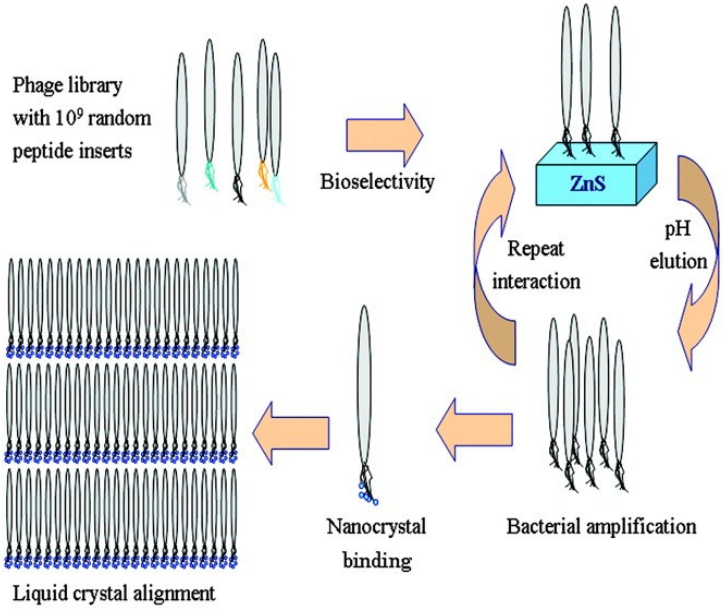
N.C. Seeman & A.M. Belcher, PNAS, 2002, *99*(Suppl. 2): 6451-6455

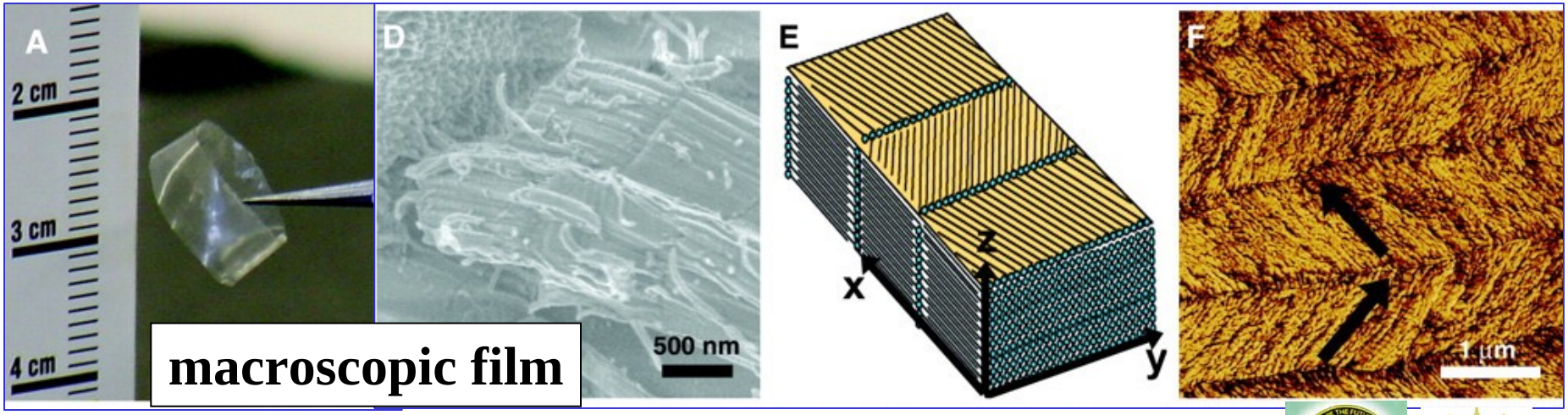
NIGMS ONR DARPA NSF

MIT

Angela M. Belcher

Phage display libraries are used to select peptides that bind to specific metals. In high concentration suspension, amplified phage self-assemble to liquid crystalline arrays. ZnS quantum dots bound to phage ends are arranged in regular 3D structures in resulting films, over cm length scales. Thus, ordered electronic, optical and magnetic materials can be assembled "bottom up."





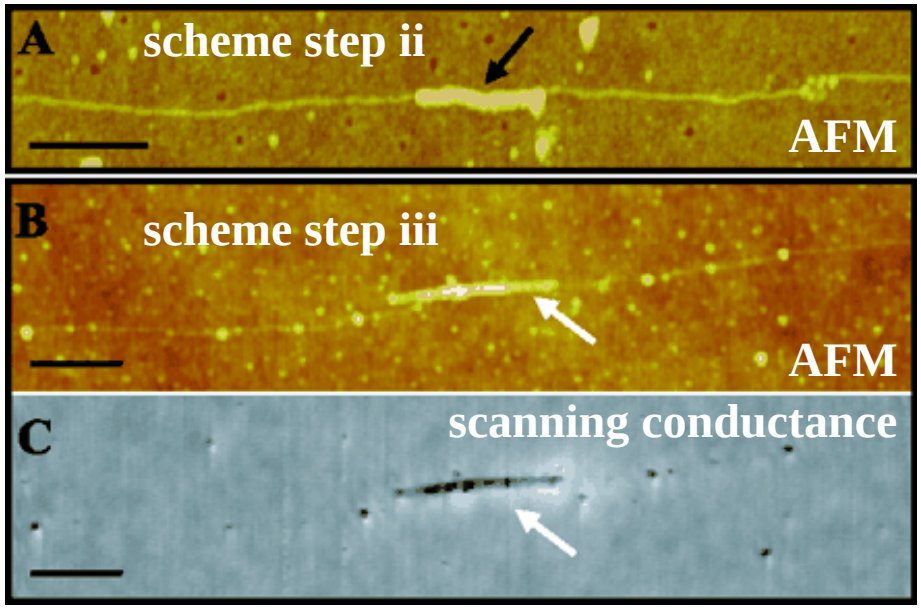
macroscopic film

S-W. Lee, et al., Science, 2002, *296*:892-895

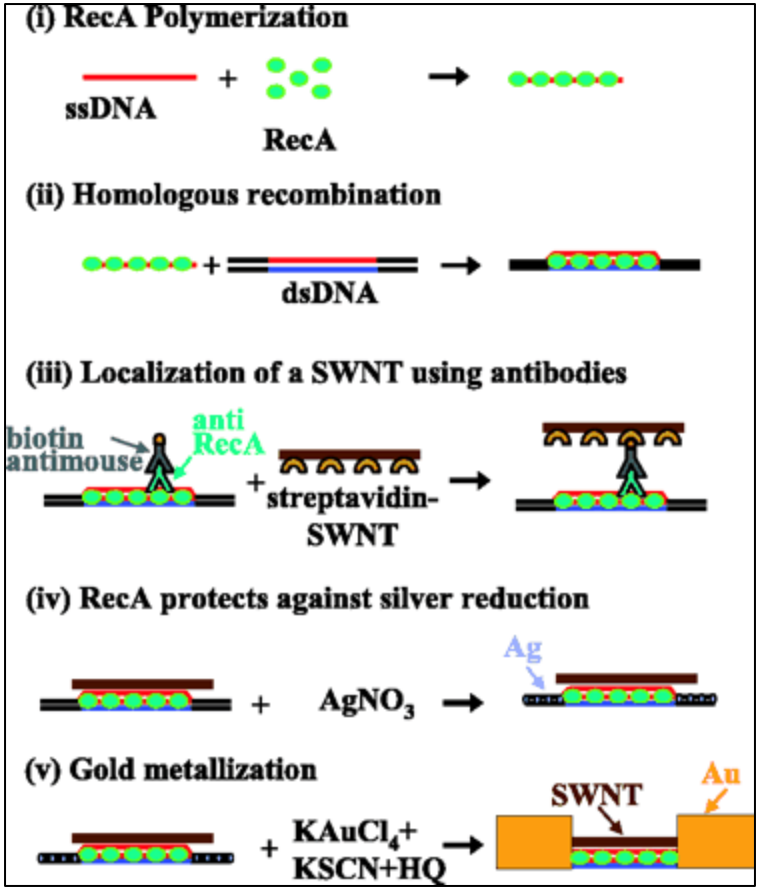
Technion-Israel Inst. of Technology

Uri Sivan & Erez Braun

Exploiting the intriguing dimensional and electrical properties of carbon nanotubes for building molecular electronics requires development of strategies for their precise localization and interconnection. Biological molecules routinely accomplish these feats in living systems and can do so in vitro.



K. Keren, et al., Science, 2003, *302*:1380-2.

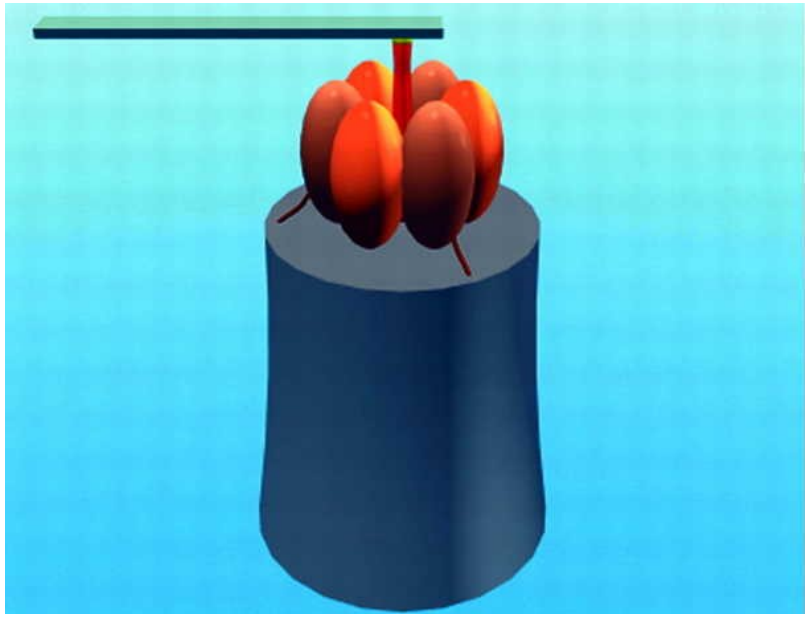


A DNA scaffold provides the address to localize a semiconducting CNT and also the template for the metallic wires contacting it. The result is a molecular electronic field effect transistor that functions at room temperature.

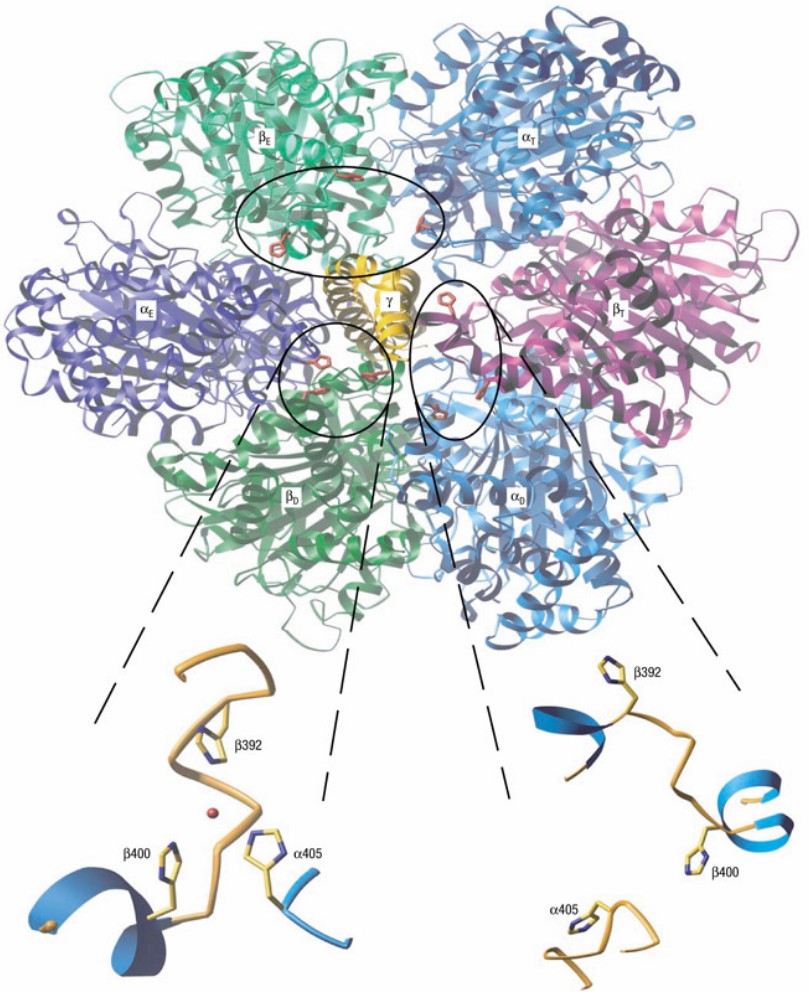
UCLA

Carlos Montamagno

A fabricated rotor was integrated with anchored F1-ATPase molecules. An ATP-independent switch (Zn-dependent, in this case) was engineered into the protein for controlling the motor.



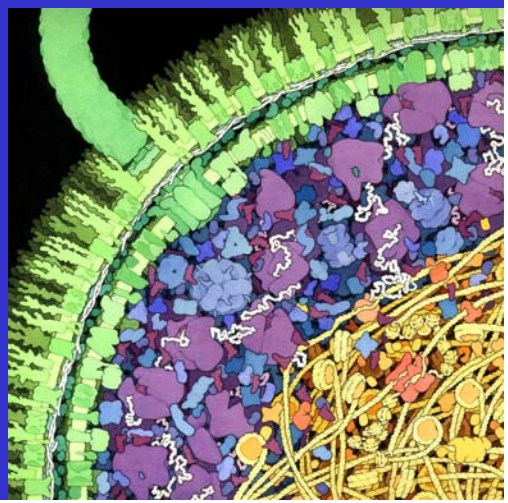
R.K. Soong, et al., Science, 2000, *290*:1555-1558



H. Liu, et al., Nature Materials, 2002, *1*:173–177

NIH Roadmap ACCELERATING MEDICAL DISCOVERY TO IMPROVE HEALTH

NANOMEDICINE ROADMAP INITIATIVE

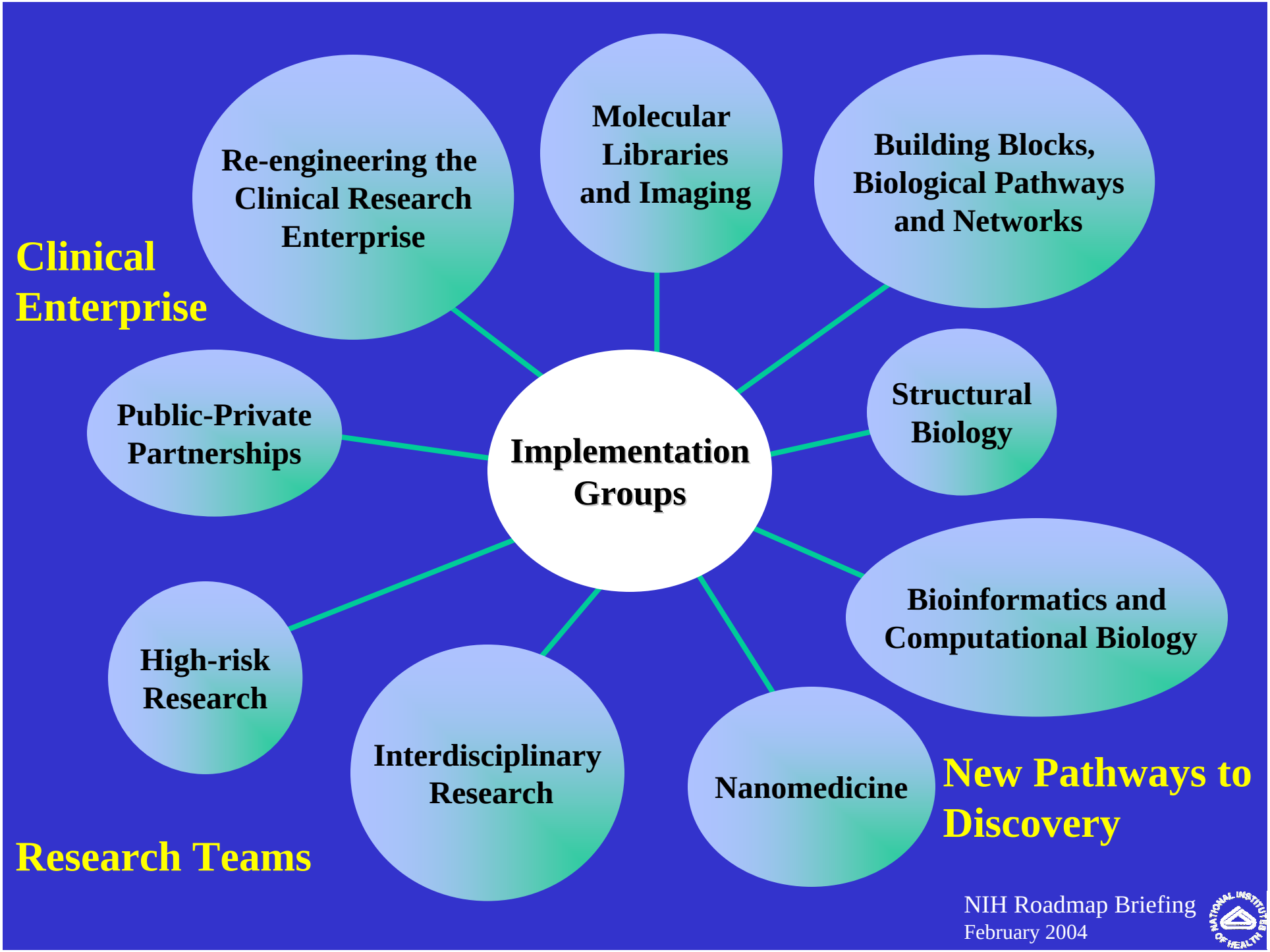


National Institutes Of Health

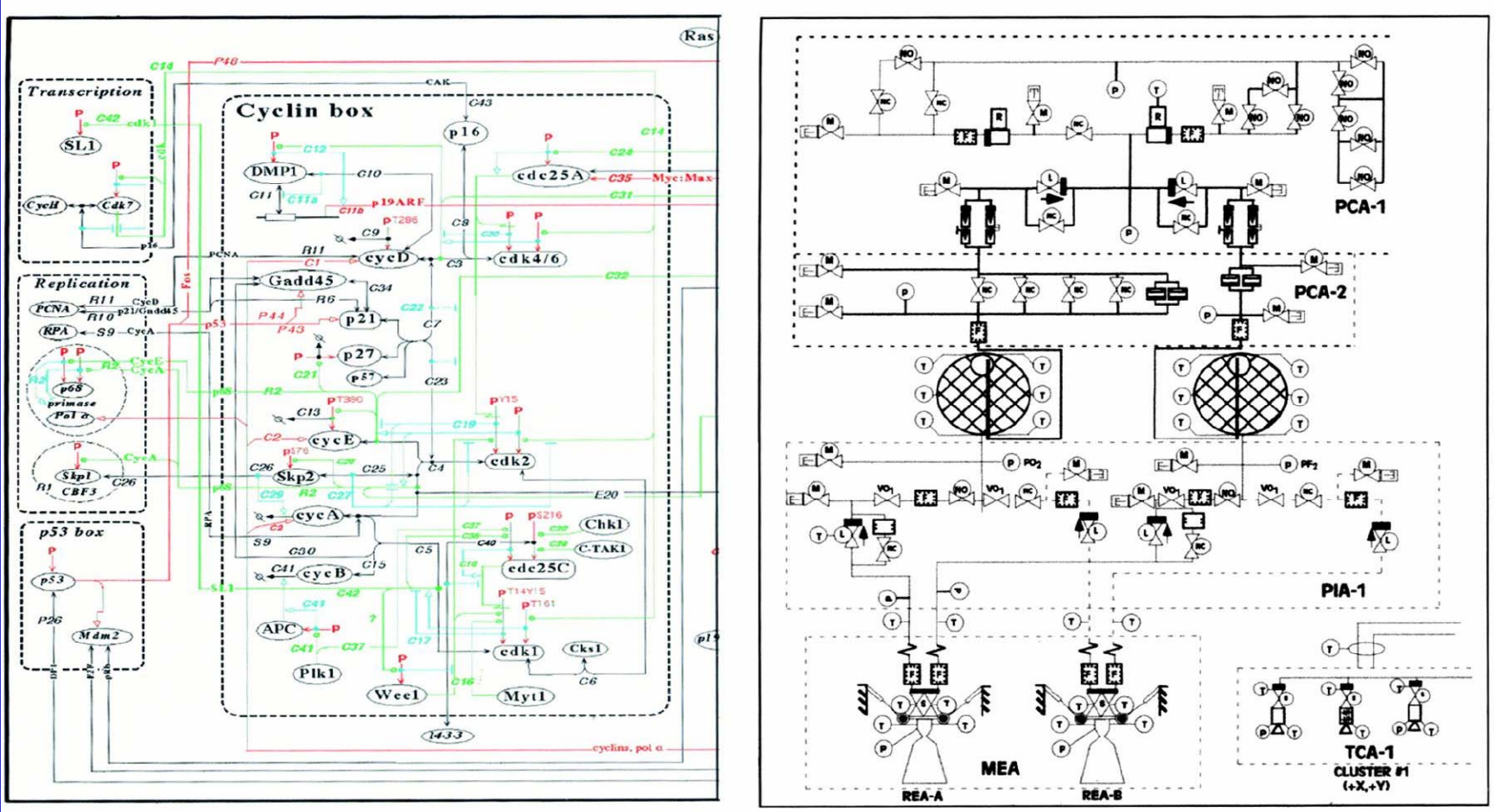
Department of Health and Human Services

Imperatives for NIH

- Accelerate pace of discoveries in life sciences
- Translate research more rapidly from laboratories to patients and back
- Explore novel approaches orders of magnitude more effective than current
- Develop new strategies: NIH Roadmap


Clinical Enterprise
Re-engineering the Clinical Research Enterprise
Molecular Libraries and Imaging
Building Blocks, Biological Pathways and Networks
Public-Private Partnerships
Implementation Groups
Structural Biology
Bioinformatics and Computational Biology
High-risk Research
Interdisciplinary Research
Nanomedicine
Research Teams
New Pathways to Discovery

Need to understand biological systems



Brent *Cell*, 2000

The Biological Data Of The Future

- Destructive
- Qualitative
- Uni-dimensional
- Low temporal resolution
- Low data density
- Variable standards
- Non cumulative

- Non-destructive
- Quantitative
- Multi-dimensional and spatially resolved
- High temporal resolution
- High data density
- Stricter standards
- Cumulative

Nanomedicine Development Centers

The NIH Vision

- Characterize quantitatively the physical and chemical properties of molecules and nanomachinery in cells;
- Gain an understanding of the engineering principles used in living cells to "build" molecules, molecular complexes, organelles, cells, and tissues; and
- Use this knowledge of properties and design principles to develop new technologies, and engineer devices and hybrid structures, for repairing tissues as well as preventing and curing disease.

From CDP Instructions…

…NIH intends that the Nanomedicine Roadmap Initiative projects should depart from established, ongoing projects and should propose truly novel approaches and break new scientific and technical ground. Our primary goal is to stimulate new ideas and directions that would not be likely to receive funding in routine grant solicitations.

Scope of Centers

- multidisciplinary -- biology, clinical, math, physics, chemistry, engineering, computational …
- biomedical focus of model system/theme -- e.g.,
  - pathway, motor system, transport
  - cell type, disease model
- toxicity, biocompatibility -- goal is to develop particles, materials and devices that can be used in vivo.
- broad (but not comprehensive) technological approach
- generality of tools (broadly applicable)
- design of tools: throughput, comprehensive measurement (à la HGP)
- operate as network of centers

NANOTECHNOLOGY RESEARCH AT NIH

BECON

CONCLUSIONS:

NIH supports nanoscience and nanotechnology research in the context of many programs, with a goal of increasing the knowledge needed to improve human health.

Nanotechnology offers technical and conceptual paths to solving important biomedical problems.

Biology offers tools and concepts applicable to nanotechnologies that will be used in non-medical fields.

Successful dovetailing of nanotechnology and biomedicine requires interdisciplinary teams, and novel research capabilities.

http://www.becon.nih.gov/becon.htm

http://www.becon.nih.gov/nano.htm

http://crisp.cit.nih.gov/

http://www.nano.gov

http:// www.nihroadmap.nih.gov

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jeff_schloss@nih.gov